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RADIOTHERAPY FOR INFLAMMATORY CONDITIONS*

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THE treatment of inflammatory processes with roentgen rays is far from new. Indeed, it goes back to about 1900. The earliest mention of the subject is to be found in papers by Freund,[7] Albers-Schönberg,[1] Gautier,[9] Rudis-Jicinsky[38] and Pusey,[35] and in the books of Williams[44] and Belot.[2] An interesting point is that some of the earliest therapeutic trials were made in this country, but they received no attention until the successful results had been repeatedly confirmed by others here and abroad.

Many physicians are unaware of the favorable influence of roentgen rays or radium on various forms of acute or chronic inflammation. Yet the therapeutic value of irradiation in inflammations has been thoroughly substantiated, and the testimony is so generally favorable that one wonders why it is not used more than it is or why, in many cases, it is employed only after other therapeutic measures have failed to yield the desired results. Perhaps the very multiplicity of inflammatory lesions for which radiotherapy has been claimed to be effective has led to a natural skepticism. Also, the many explanations which have been advanced to account for the favorable action of roentgen rays or radium on inflammations have probably led many physicians to discredit the evidence or to ascribe the favorable reports to enthusiasm or to psychic factors. Indeed, without a convincing explanation it would be difficult to believe that the same agent could be therapeutically effective against so many different forms of inflammation. And yet the reason appears to be simple and to rest on abundant experimental evidence.

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Others who have heard or read of the therapeutic possibilities of irradiation in inflammatory processes hesitate to make use of the method because they fear deleterious effects on the skin or gastrointestinal disturbances such as are observed in connection with the treatment of malignant tumors. When treating neoplasms the aim is to deliver the largest dose compatible with the integrity of the surrounding tissues. When treating inflammatory lesions, on the contrary, only small or moderate doses are employed. Doses that might strain the tolerance of the skin are unnecessary and should be avoided as potentially dangerous. For acute inflammations especially, the doses required are so small that the skin or the gastrointestinal tract cannot possibly be affected. Hence any fear on this score is unfounded.

ACUTE INFLAMMATIONS

Many varieties of acute inflammation yield rapidly to a small dose of roentgen rays. By a small dose is meant one representing less than half the tolerance dose of the skin; a dose as small as a fourth of the so-called erythema dose, or even less, is often sufficient, but this may vary somewhat according to the character and stage of the lesion in a given case. A significant point is that the more acute the inflammation, the smaller the dose of rays required. With such small doses there can be no question of cutaneous or systemic reaction; therefore weak and febrile patients can be treated without danger. In most cases a single exposure is sufficient, but occasionally it may be advisable to repeat the treatment a few days later. This is particularly true when the initial dose has been exceptionally small or when the region treated has not been wide enough.

Among the acute inflammatory conditions in which the therapeutic value of irradiation has been

established are furuncle, carbuncle, abscess, cellulitis and phlegmon, onychia and paronychia, acute adenitis, pneumonia, acute parotitis and erysipelas. In other forms of acute inflammation, such as sinusitis, otitis and mastoiditis, pelvic infection, osteomyelitis and gas-bacillus infection, a considerable body of evidence indicates an equally favorable response in many cases, but more controlled evidence will be required to be convincing.

Pyogenic Infection. When irradiated early, during the stage of maximal leukocytic infiltration, many lesions due to pyogenic cocci do not suppurate; their evolution is arrested and they undergo spontaneous resolution. Therefore the treatment is most effective when other methods of treatment are least effective; it is painless, and does not interfere with the activities of the patient. Pain is often relieved in a few hours, but sometimes the relief may be preceded by exacerbation for a brief period. Hot or other dressings are often unnecessary, or the period during which they must be applied is shortened. Treatment after suppuration has set in tends to hasten the suppurative process, the duration of which may thus be more or less diminished. Hence the patients should be kept under close observation so that, if necessary, the surgeon may provide adequate drainage at the proper time. But acute pyogenic inflammations do not always respond so favorably; in a minor proportion of cases they yield little or not at all. This is especially true when the treatment is started long after the onset, that is, late in the course of the inflammation, when exudates have undergone organization and when some degree of connective-tissue proliferation has occurred.

Pneumonia. As early as 1905 and 1906, Musser and Edsall[34] and Edsall and Pemberton[6] observed and reported the strikingly favorable influence of a small dose of roentgen rays in 4 cases of delayed resolution of lobar pneumonia. Every other therapeutic measure having failed to improve the pulmonary condition of the patients, roentgen irradiation was tried as a last resort. Within twenty-four hours after exposure, resolution of the pneumonic exudate set in and proceeded rapidly, and the patients recovered. These observations were subsequently confirmed by Quimby and Quimby,[36] Krost[24] and Torrey.[41] In fact, the Quimbys were so impressed by the rapid influence of irradiation in 10 cases that they were impelled to testify that "no pathologic process in the body responds quicker to an x-ray exposure than the non-resolution following pneumonia." Since then, Heidenhain and Fried,[13] Holzknecht,[20] Merritt and McPeak[33] and others have observed favorable action of roentgen rays on postoperative pneumonia, as well as on pneumonia unrelated to surgical intervention, in a large percentage of cases in which the treatment was employed. Naturally, the best results are to be obtained from early treatment. As pointed out by Musser and Edsall, irradiation cannot be expected to have much effect once the pneumonic inflammation has become organized or when the treatment is given shortly before impending death.

Acute Parotitis. Every surgeon is aware of the sinister character of that form of acute parotitis which arises as a complication of certain operations, especially those on the large intestine, and of the high mortality associated with it. The first record of the favorable effect of irradiation on this disease appears to have been made by Heidenhain,[12] who found that the inflammation reacted much as do other acute inflammatory processes. Rankin and Palmer[37] found that a moderate dose of radium, applied soon after the onset, caused the inflammation to subside in most cases within twenty-four to forty-eight hours. Moreover, suppuration usually did not occur, and the mortality was correspondingly reduced. Radium is sometimes preferable because the treatment can thus be given without disturbing the patient. When portable roentgen therapeutic apparatus is available, however, this is an advantage because the necessary dose can be given in much less time than with radium.

Erysipelas. When erysipelas does not complicate diabetes or nephritis, roentgen irradiation is usually followed by prompt abatement of the fever and recession of the lesions. This is especially true when the patients are adults and when the treatment is given early. In children, for some unknown reason, the disease does not respond quite so well. In some cases, after an initial period of improvement, the inflammation may again become active, and additional treatment may be required to arrest the process. When this happens, it is usually because the initial treatment was confined too closely to the apparent limits of visible involvement. Too much stress cannot be laid on the importance of including in the field of irradiation a wide zone of apparently normal tissue around the lesion. A single dose, corresponding to 100 or 200 r, generated at 130 or 140 kilovolts and filtered through 4 mm. of aluminum, is usually sufficient.

Favorable results may also be obtained by exposing the affected region to an erythema or blistering dose of ultra-violet rays. A possible disadvantage is that during the period of cutaneous reaction to treatment it may be difficult to know what is disease and what represents reaction. Roentgen irradiation has no such disadvantage; the dose required does not cause reactive inflammation.

Other Acute Inflammations. Other acute inflammations have been found to yield equally well to roentgen irradiation. Some years ago Granger[10] reported that in certain cases of acute mastoiditis in which the mastoid region had been exposed to small doses of roentgen rays for diagnostic purposes the inflammation had subsided and an operation had been unnecessary. Similar reports have appeared since then, but some of these have been rather too casual to be convincing. I am not aware that the possible therapeutic advantage of irradiation in this condition has ever been given a serious and thorough test. This is unfortunate, because if acute mastoiditis should be found to yield as do so many other forms of inflammation, many patients might be saved some of the pain, mental stress and cost of hospitalization associated with operations for the condition. Moreover, this possibility could be tested without jeopardizing the interests of the patients in any way.

In 1936, Kelly and Dowell[21] reported that favorable results had been obtained in cases of gas-bacillus infection. Since then, these authors have published several additional reports based on a larger number of cases. According to them, the only patients who died were those in whom an affected extremity had been amputated. The number of cases included in their latest report[22] is now sufficient to command attention, especially since they appear to have succeeded in reducing the mortality to less than 10 per cent when amputations were necessary, and to less than 5 per cent when they were not. If the experience of others should confirm the results obtained by Kelly and Dowell, roentgen therapy might be shown to be a great boon to patients afflicted with this virulent form of infection.

In treating inflammations caused by such virulent bacteria, Kelly and Dowell have found it advantageous to use doses as small as 100 r and to repeat them daily or twice daily for three or four days. Although the reason why this procedure is more effective is not clear, it is possible that when the infecting bacteria have a high degree of virulence a single irradiation does not influence a sufficient number of circulating leukocytes to overcome the infection. But when irradiation is repeated daily or twice a day for three or four days, the number of leukocytes acted on by the rays must necessarily be much greater, and this may account for the greater efficacy of this method in the treatment of gas-bacillus infection. Inasmuch as streptococcal infections often assume a virulent form and leukocytic infiltration is often slight or wholly lacking, it is possible that the same method of small doses repeated daily or twice daily for three or four days would have a similar advantage.

Type of Rays. The quality of the rays is of secondary importance. Favorable results may be obtained with rays generated at 100, 140 or 200 kilovolts. If in most cases the results obtained with rays generated at 130 or 140 kilovolts seem superior to those obtained with rays generated at a higher potential, this is almost certainly not due to any specific action of rays of different wave length, but probably to a difference in absorption by the inflamed tissues. A larger proportion of rays of medium wave length than of rays of short wave length is absorbed in the first few centimeters of tissue. Therefore, since the majority of the inflammatory conditions mentioned are near the surface, the advantage, so far as maximal absorption at the desired level is concerned, would seem to favor rays of medium wave length. When the inflammation is deep in the chest, rays of short wave length might be preferable. However, since the most effective dose is small, this theoretical advantage is not an important factor.

Chronic Inflammations

For years it has been known that many forms of chronic inflammation are favorably influenced by roentgen irradiation. Among these may be mentioned numerous varieties of chronic inflammation of the skin in which the therapeutic value of radiotherapy is conceded by experienced dermatologists. Other chronic inflammatory processes which may be cited are tuberculous adenitis, peritonitis, keratitis and iritis; actinomycosis and blastomycosis; trachoma in its early stages; and active, infectious arthritis. Two features which characterize this type of irradiation are that the dose of roentgen rays must be larger than that used for acute inflammations and that treatment must be repeated at intervals for some time. By a larger dose is meant a dose varying between 50 and 80 per cent of the tolerance dose when given at one time or, in international units, between 300 and 500 r, according to the conditions of irradiation. Rays generated at 120 or 140 kilovolts and filtered through 4 or 6 mm. of aluminum are usually adequate. Rays generated at higher potentials can be used with approximately equal effect. For skin diseases, unfiltered rays or rays filtered through 2 mm. of aluminum and generated at 80 or 100 kilovolts are generally preferable. The treatment of chronic inflammatory lesions with maximal (erythema, tolerance or tumor) doses is bad practice, and should be avoided as potentially dangerous. Since treatment must be repeated at intervals for varying periods, the use of maximal doses may lead to undesirable effects or, by superimposing a

reactive inflammation, may cause the original inflammation to spread rather than to abate.

Tuberculous Processes. Although considerable variation may be observed in different cases, the effect of irradiation on tuberculous processes is characteristically slow. In tuberculous adenitis the affected region must be irradiated every three or four weeks for three to twelve months. When calcification is absent, the inflamed nodes gradually recede and may disappear completely, or may remain as small fibrous granules. Unless abundant, caseous material may be absorbed or may be replaced by calcium. When suppuration occurs drainage may be advisable, but sometimes the pus can be withdrawn through a needle of large bore, which should be introduced not through the thinnest part of the fluctuant region, but to one side through more substantial tissue, so as to avoid the formation of a sinus. The extensive surgical procedures formerly in vogue are now seldom necessary. The resolution of tuberculous lesions appears to be hastened by supplementing periodic roentgen irradiation with daily exposure of the entire body to graduated doses of sunlight or to ultra-violet rays generated artificially. Ultra-violet irradiation confined to the affected region is usually a waste of time.

Much the same may be said of tuberculous peritonitis. An important consideration is that the entire abdominal cavity should be irradiated as uniformly as possible. This can best be done by dividing the anterior half of the abdomen from the level of the diaphragm to that of the pubic region into four fields, with the navel as the common center; the posterior half should be divided into four corresponding fields.

Radiotherapy is also an effective method of treating tuberculosis of the cornea or iris. The lesions recede more rapidly after exposure to roentgen rays than do similar lesions in other parts of the body. The dose of roentgen rays should never exceed three fourths of a minimal erythema dose; a larger dose, especially in children, may lead to epithelial degeneration of the crystalline lens and to cataract formation.

Actinomycosis. When actinomycosis affects the face, mouth or other superficial structures, roentgen or radium irradiation, supplemented by the internal use of large doses of iodides and sometimes by simple surgical drainage of an abscess, is the most effective therapeutic measure, and a large proportion of patients can thus be permanently cured.

Not infrequently actinomycotic inflammation arises in the intestine, especially the lower part of the small intestine, where it is often mistaken for simple or suppurative appendicitis. In many cases one or more operations are performed, and the true character of the process is not recognized. This is unfortunate because, if the lesion is actinomycotic in character, exploratory maneuvers or any measures beyond simple drainage of an abscess serve only to spread the infection. Thorough exposure of the entire abdomen (front and back) to about three fourths of an erythema dose of roentgen rays, repeated every three or four weeks, may be followed by substantial improvement and sometimes by complete and permanent cure. But when the infection has extended to the respiratory tract (bronchi, lungs and pleura), more than slight and temporary improvement is not likely to be obtained with any method of treatment.

Trachoma. Trachoma is characterized by conjunctival granulations composed largely of lymphocytes. These granulations are gradually replaced by connective tissue, and the eyelids become sclerosed and distorted. As early as 1902 and 1903, Mayou.[30, 31] Stephenson and Walsh[39] and Cassidy and Rayne[4] made the discovery that, in some cases, the trachomatous granulations receded after exposure to roentgen rays, and that the patients were cured. Subsequently, Thielemann,[40] Cochard[5] and Meldolesi and Sabbadini[32] confirmed the favorable influence of radiotherapy. Sometimes the lesions recurred later, but resumption of treatment caused them to retrogress and disappear; this probably meant that the initial treatment had not been continued long enough. The evidence furnished by the group of writers last mentioned indicates that the action of the rays is greatest during the early stages of the granular form of the disease and least during the late stages, when the granulations have been replaced by connective tissue.

Chronic Infectious Arthritis. In many cases roentgen irradiation relieves pain and reduces swelling, and the functional disability diminishes. As might be expected, the degree of improvement varies considerably in different patients. The best results require repeated treatment and are obtained in cases in which the inflammation is active. Incidentally, a useful indication of active inflammation is tenderness. When the inflammatory deposits have become largely or completely organized, little improvement is to be expected. Of course, focal infection must not be neglected, irrespective of irradiation.

Bronchiectasis. Recently Berck and Harris[3] reported having treated with roentgen rays 30 patients with bronchiectasis, of whom 19 are said to have derived more or less pronounced improve-

ment. Here again an opinion about the value of irradiation will have to await corroborative testimony. However, the care with which the cases appear to have been selected and the degree of improvement obtained in many of them make this report seem worthy of attention.

General

One consideration cannot be stressed too much, and the inability of some radiologists to obtain satisfactory results is often due to their failure to realize its importance. This consideration is that, in chronic inflammations generally, treatment must be continued for a long time. Even after the lesions and symptoms have disappeared or have ceased to be active, it is wise to treat the patient once or twice more. The more chronic the lesion, the more essential is this precaution. As examples I need only cite tuberculous adenitis, peritonitis, arthritis and synovitis. The response of tuberculous lesions to roentgen irradiation varies considerably from one patient to another, but in general it is characteristically slow. When treatment is stopped too soon, what might have been an excellent and permanent result is spoiled; after a period of apparent arrest, the tuberculous process becomes active again, and resumption of treatment may not be so effective as before. Greater persistence in the first instance is usually the best policy.

When dealing with acute or chronic inflammatory lesions, a most important point is that the concept of maximal, tolerance or tumor doses must be abandoned. Not only are they less effective, but they are actually dangerous. To employ such doses in treating inflammatory conditions constitutes a loss of electrical energy, a gross waste of time on the part of the personnel as well as that of the patient and an unwarranted increase in cost. But, still more important, there is danger of inducing in the affected tissues an inflammatory reaction independent of that which is already present, and this might readily lead to spread rather than resolution of the infection. The principles of sound treatment are thus violated. This probably explains why some radiologists have failed to obtain the favorable results which should follow proper treatment. Furthermore, the possibility of spreading the infection by excessive doses is not the only danger. Experiments on animals carried out by Lacassagne and Vinzent[25–29] have shown that, when acute inflammatory lesions induced by injecting *Streptobacillus caviae* into rabbits were exposed to doses of roentgen rays such as are used in the treatment of malignant processes, in a considerable proportion of animals sarcomas subsequently developed in the same region.

Mode of Action

Acute Inflammations. Numerous experiments have long since made it clear that most bacteria are not directly influenced to a perceptible degree by doses of roentgen rays or radium such as are commonly employed in treating human beings. To attribute the favorable effect of irradiation to a bactericidal action of the rays, therefore, would be to maintain an untenable hypothesis. Certainly there is little ground for the assumption that irradiation increases the production of antibodies. On the contrary, the experiments of Hektoen[17–19] and others indicate that irradiation tends to diminish the formation of antibodies. Nor does the evidence now available justify one in assuming that any difference in the quality of the rays has a direct effect on the result, but the quality of the rays may and probably does have an indirect effect because it influences the proportion of rays absorbed at different depths beneath the surface.

Anyone who has had an extended experience with radiotherapy for acute inflammations cannot have failed to be impressed by the prompt relief of pain and the rapid resolution of the lesions when treated early, as well as by the acceleration of suppuration in lesions treated later; by the fact that acute inflammations of different kinds respond at about the same rate to a given dose when treated at a corresponding stage; and by the circumstance that a small dose of rays is sufficient to produce this effect. Since irradiation acts in the same way and within the same time on so many forms of acute inflammation, it seems logical to conclude that the lesions themselves must have some common factor. This factor appears to be the radiosensitiveness of certain cells which are a more or less prominent feature of the majority of acute inflammations.

Pyogenic infections in general are characterized by varying degrees of leukocytic infiltration. By accumulating leukocytes, chiefly lymphocytes, polymorphonuclear cells and eosinophils, around one or more clusters of bacteria, the body attempts to localize the infection, destroy the invading organisms and neutralize their toxic products. The leukocytic infiltration also appears to be Nature's method of intensifying the production of antibodies. An additional factor is hyperemia, which facilitates the mobilization of leukocytes. Of some acute inflammations, especially those caused by streptococcal infection, local infiltration by leukocytes is not a prominent feature. Against infections of this kind the body apparently defends itself by a general reaction of the leukocytes in the circulating blood.

Experiments on a large number of animals of different species and observations on human beings

as to the effect of roentgen rays and radium on different kinds of cells and tissues have proved conclusively that each variety of cell has a specific range of sensitiveness to irradiation. Some are extremely sensitive, even to small doses, while others are not influenced by doses many times larger. Moreover, these experimental and clinical investigations have demonstrated that the most sensitive of all cells are the lymphocytes in the spleen, lymph nodes, lymph follicles, thymus gland, circulating blood and bone marrow. The polymorphonuclear and eosinophilic leukocytes are also sensitive, but their susceptibility to irradiation is slightly less than that of the lymphocytes. When the entire body of an animal is exposed to a moderate dose of roentgen rays or radium, the majority of the organs remain free from perceptible abnormalities, but the spleen, lymph nodes and intestinal lymph follicles show a destruction of lymphocytes, the degree of which varies according to the dose of rays and the interval between irradiation and the removal of the tissue.

As observed by Heineke,[14–16] the disintegration of lymphocytes was characterized by disorganization and fragmentation of the nuclear chromatin of the cells and by scattering of the fragments of chromatin between the remaining intact cells and in the spaces of the reticular stroma, where the fragments gathered into clumps or balls. The latter were gradually taken up by some of the reticula[illegible] which assumed a phagocytic property and s[illegible]led as the amount of ingested chromatin debris increased. This process was associated with a progressive reduction in volume of the affected lymphoid structures. Identical changes were observed in the lymphoid tissue of the vermiform appendix and in the bone marrow. The destruction of lymphocytes in the spleen and lymph nodes was often so great that most of the malpighian corpuscles or lymph follicles could be recognized only by the blood vessels and by the concentric arrangement of the stroma. A small percentage of lymphocytes appeared to resist the action of the rays. After a number of hours, the phagocytic reticular cells (macrophages) themselves began to disappear. The chromatin debris ingested by the phagocytes appeared to undergo intracellular digestion, because the number and size of the ingested fragments diminished steadily. Two or three days after irradiation, degenerative alteration of others cells, notably the polymorphonuclear leukocytes and eosinophils, also became perceptible, and many of these cells disappeared from the splenic pulp and bone marrow. From ten days to three weeks later more or less regeneration of the lymphoid tissue became evident.

Since the time of these observations Heineke's results have been confirmed by many investigators, including Krause and Ziegler,[23] Fromme,[8] Hall and Whipple,[11] Warthin,[43] Tsuzuki[42] and many others. Warthin's description of the effect of roentgen rays corroborated the observations of Heineke in every particular, except that by examining the tissue soon after irradiation Warthin found unmistakable evidence of the disintegration of lymphocytes within fifteen minutes after exposure of the animals to the rays, and a continuation of the cellular degeneration for several days. Similar effects have been obtained with radium. Other investigators have demonstrated that the lymphocytes in the circulating blood are equally sensitive to irradiation and that the circulating polymorphonuclear and eosinophilic leukocytes are only slightly less sensitive than the lymphocytes.

The rate at which the varieties of leukocytes mentioned are destroyed by irradiation under experimental conditions corresponds closely to the rate at which acute inflammations subside after exposure to a suitable dose of roentgen rays or radium. The only other cells in the body which are affected at anything like the same rate are the mucus-secreting epithelial cells in the salivary glands, the bronchi and the intestine; but since these cells cannot play any part in the majority of inflammatory processes, they may be excluded from consideration.

In circumscribed inflammations the significant role of lymphocytes, polymorphonuclear cells and eosinophils in the defense of the organism against infection and the sensitiveness of these cells to irradiation make it appear likely that when an inflammatory lesion is irradiated, the rays act mainly by destroying a proportion of the leukocytes infiltrating the lesion or circulating in the blood vessels which supply the affected region. This view is corroborated by the rapidity with which the symptoms often abate and the physical signs disappear. Moreover, microscopic examination of irradiated inflammatory lesions has repeatedly shown destruction of leukocytes, especially lymphocytes, to be the outstanding feature observed. It seems logical to conclude, therefore, that destruction of leukocytes is the primary and direct effect of irradiation. As a result of the disintegration of infiltrating leukocytes the antibodies, ferments and other protective substances which these cells contain are liberated in the surrounding tissue spaces, where they become mixed with the tissue fluids. It is also probable, as the experimental evidence indicates, that the next step is an increase in phagocytosis by reticular cells which become macrophages. No doubt other intimate, secondary or indirect effects related to cell metabolism are pro-

duced, but the precise character and significance of these effects are not clear.

Since leukocytic infiltration is an outstanding factor in the defense against infection, the natural question is why destruction of a large number of leukocytes infiltrating such lesions may not do more harm than good. The only answer is that, after small or moderate doses, no one has yet submitted any evidence of ill effects. The influence of irradiation has always been favorable or the rays have failed to alter the course of the inflammatory process.

From the foregoing considerations, therefore, it seems not unreasonable to assume that irradiation, by destroying some of the infiltrating leukocytes, causes the protective substances in these cells to be liberated and to be made even more readily available for defensive purposes than when they were in the intact cells. This and the increase in phagocytosis which follows the disintegration of the cells represent the main effects of exposure to roentgen rays or radium, and probably explain the usually favorable action of these agents.

All the clinical circumstances indicate that inflammatory lesions respond to irradiation in proportion to the degree of leukocytic infiltration. In favor of this view are the experimentally proved radio-sensitiveness of lymphocytes, polymorphonuclear leukocytes and eosinophils, the fact that the rate of regression of acute inflammations corresponds to the rate at which these cells are known to be destroyed by irradiation and the fact that these cells are the only ones commonly found in inflammatory lesions that could be affected at such a rapid rate by small or moderate doses. Other circumstances pointing in the same direction are that radiotherapy is more beneficial during the infiltrative stage and less so during the suppurative stage, and that, although the majority of lesions yield quickly to treatment, some respond less rapidly or do not respond at all. Variation in the degree of leukocytic infiltration of different lesions of the same character or of similar lesions of different character is a well-known pathological fact. Therefore, the degree of leukocytic infiltration must influence the action of the rays, because the rays can destroy leukocytes only in proportion to the number of these cells. This is undoubtedly related to and probably explains the fact that, while many inflammatory lesions are influenced favorably, some react much less or not at all.

When the inflammation is not confined to a small region but is extensive or diffuse rather than circumscribed, and when leukocytic infiltration is not a pronounced feature, as in erysipelas, the rays probably act in a somewhat different manner. Under these circumstances, the smaller number of infiltrating leukocytes should prevent the rays from having the same local effect, unless some compensatory mechanism enters into play. Evidence of such a mechanism in erysipelas has not yet been demonstrated, but that it exists is indicated by the action of roentgen rays in other diseases. In bronchial asthma, for example, irradiation of the spleen or of other parts of the body remote from the bronchi and lungs is often followed by more or less striking relief from symptoms. What probably takes place is a destruction of leukocytes in the spleen and in the large mass of blood circulating through this organ. Then the cellular debris and the contents of the destroyed cells find their way into the general circulation, where they have been shown to produce a protein-like reaction. In inflammations that are not circumscribed and in which leukocytic infiltration is comparatively slight, the affected region is hyperemic and the vessels are more or less gorged with blood. Wide exposure of such a region to a small dose of rays undoubtedly causes many leukocytes to disintegrate, and the contents of the destroyed cells are liberated into the blood and throughout the tissue spaces. And the destruction of leukocytes is probably followed by changes similar to those described in connection with more limited inflammations. At least this would seem to be the most logical conclusion. Any other assumption would be inconsistent with the known facts and with the clinical behavior of this kind of inflammation.

Recently, a well-known radiologist told me that he thought the action of the rays must be on the hyperemia and the edema. According to this conception the rays would act on the serum in the blood or tissues and not on the cells. If this were true, the action of the rays would necessarily be chemical or physicochemical. But where is the evidence to support such an idea? I am not aware of any. On the contrary, the evidence in favor of a direct and major action on infiltrating leukocytes is so abundant that anyone who takes the trouble to analyze and correlate it cannot fail to be impressed with its probable significance.

Chronic Inflammations. In order to understand the influence of irradiation on chronic inflammations it is necessary to bear in mind a few essential points. Depending on their character and on the etiologic factors which produce them, such lesions are characterized by varying degrees of leukocytic infiltration, connective-tissue proliferation and caseous, calcareous or hyaline degeneration. Moreover, the clinical effect of irradiation is slow, and maximal improvement or cure requires repeated treatment at intervals. From what

is known about the action of roentgen rays and radium on different varieties of cells and tissues, it seems most likely that these factors are closely related. Since cheese and chalk are products of cellular degeneration, they should not be influenced by irradiation, and this is precisely what is observed in practice. As we have already seen, the varieties of leukocytes which are such an important feature of inflammatory infiltration are exceptionally sensitive to roentgen rays or radium. Connective tissue cells, on the contrary, are comparatively resistant to irradiation; they are even less sensitive than the epithelium of the skin. In this respect the difference between lymphocytes or polymorphonuclear leukocytes and connective tissue cells is tremendous.

Analysis and correlation of these several factors would seem to furnish a satisfactory explanation of the effect of radiotherapy on chronic inflammatory processes. The greater the degree of leukocytic infiltration in proportion to connective-tissue proliferation, the more marked and the more rapid is the influence of the treatment, and vice versa. If tuberculous lesions are taken as an example, it is well known that the effect of irradiation is greater during the infiltrative phase of the tubercles, when leukocytic infiltration is most pronounced, than it is when the leukocytic infiltration has diminished and has passed into an advanced stage of caseous degeneration or of repair by connective tissue or by calcification. It is probable, therefore, that leukocytic infiltration, on the one hand, and connective-tissue proliferation, on the other, act in opposite directions, the former tending to increase the effect of irradiation and the latter to diminish or retard this effect. This conclusion is in complete harmony with the experimental evidence and with all the clinical observations which have been recorded.

REFERENCES

1. Albers-Schönberg: Beitrag zur therapeutischen Verwendung der Röntgenstrahlen in der Behandlung des Lupus. Fortschr. a. d. Geb. d. Röntgenstrahlen **1**:72-75, 1897-1898.
2. Belot, J.: *La radiothérapie, son application aux affections cutanées.* 520 pp. Paris Thesis, No. 426, 1904.
3. Berck, M., and Harris, W.: Roentgen therapy for bronchiectasis. J. A. M. A. **108**:517-522, 1937.
4. Cassidy, H. F., and Rayne, F. C.: Trachome chronique très amélioré par les rayons X. Ann. d'électrobiol. et de radiol. **6**:617-619, 1903.
5. Cochard, M.: La radiothérapie du trachome. Lyons Thesis, No. 128, 1921.
6. Edsall, D. L., and Pemberton, R.: The use of the x-rays in unresolved pneumonia. Am. J. M. Sc. **133**:286-297, 1907.
7. Freund, L.: Ein mit Röntgen-Strahlen behandelter Fall von Naevus pigmentosus piliferus. Wien. med. Wchnschr. **47**:428-434, 1897.
8. Fromme, G.: Ueber die allgemeine Wirkung der Röntgen- und Radiumstrahlen. Ztschr. f. Geburtsh. u. Gynäk. **79**:579-613, 1917.
9. Gautier: Traitement de l'acné et de la couperose par les rayons X. Cong. internat. de méd. **4**:385, 1899.
10. Granger, A.: The treatment of infections of the mastoids of infants, when there is no sign of destruction present, with fractional doses of the roentgen rays. New Orleans M. & S. J. **84**:111-113, 1931.
11. Hall, C. C., and Whipple, G. H.: Roentgen-ray intoxication: disturbances in metabolism produced by deep massive doses of the hard roentgen rays. Am. J. M. Sc. **157**:453-482, 1919.
12. Heidenhain, L.: Röntgenbestrahlung und Entzündung. Strahlentherapie **24**:37-51, 1926.
13. Heidenhain, L., and Fried, C.: Röntgenbestrahlung und Entzündung. Arch. f. klin. Chir. **133**:624-665, 1924. Röntgenstrahlen und Entzündung. Klin. Wchnschr. **3**:1121, 1924.
14. Heineke, H.: Ueber die Einwirkung der Röntgenstrahlen auf Tiere. München. med. Wchnschr. **2**:2090-2092, 1903.
15. *Idem:* Zur Kenntnis der Wirkung der Radiumstrahlen auf tierische Gewebe. München. med. Wchnschr. **2**:1382-1384, 1904.
16. *Idem:* Experimentelle Untersuchungen über die Einwirkung der Röntgenstrahlen auf innere Organe. Mitt. a. d. Grenzgeb. d. Med. u. Chir. **14**:21-94, 1905.
17. Hektoen, L.: The influence of the x-ray on the production of antibodies. J. Infect. Dis. **17**:415-422, 1915.
18. *Idem:* Further studies on the effects of the roentgen ray on antibody-production. J. Infect. Dis. **22**:28-33, 1918.
19. *Idem:* Further observations on the effects of roentgenization and splenectomy on antibody production. J. Infect. Dis. **27**:23-30, 1920.
20. Holzknecht, G.: Roentgen treatment of spontaneous post-traumatic and post-operative coccus infections and suppurations. Am. J. Roentgenol. **15**:332-336, 1926.
21. Kelly, J. F., and Dowell, D. A.: Present status of the x-rays as an aid in the treatment of gas gangrene. J. A. M. A. **107**:1114-1118, 1936.
22. Kelly, J. F.; Dowell, D. A.; Russum, B. C., and Colien, F. E.: The practical and experimental aspects of the roentgen treatment of *Bacillus welchii* (gas gangrene) and other gas-forming infections. Radiology **31**:608-619, 1938.
23. Krause, P., and Ziegler, K.: Experimentelle Untersuchungen über die Einwirkung der Röntgenstrahlen auf tierisches Gewebe. Fortschr. a. d. Geb. d. Röntgenstrahlen **10**:126-182, 1906.
24. Krost, G. N.: Unresolved pneumonia in children: treatment with roentgen ray. Am. J. Dis. Child. **30**:57-71, 1925.
25. Lacassagne, A.: Tumeurs malignes provoquées, chez le lapin, par l'irradiation de foyers inflammatoires. Compt. rend. Acad. d. sc. **196**:69-71, 1933.
26. *Idem:* Conditions dans lesquelles ont été obtenus, chez le lapin, des cancers par action des rayons X sur des foyers inflammatoires. Compt. rend. Soc. de biol. **112**:562-564, 1933.
27. *Idem:* Cancers produced in rabbits by the action of x-rays upon inflammatory lesions. Brit. J. Radiol. **6**:689-691, 1933.
28. Lacassagne, A., and Vinzent, R.: Action des rayons X sur un foyer infectieux local, provoqué chez le lapin par l'injection de *Streptobacillus caviae.* Compt. rend. Soc. de biol. **100**:247-249, 1929.
29. *Idem:* Sarcomes provoqués chez des lapins par l'irradiation d'abcès a *Streptobacillus caviae.* Compt. rend. Soc. de biol. **100**:249-251, 1929.
30. Mayou, M. S.: A case of trachoma treated by x-rays. Tr. Ophth. Soc. U. Kingdom **22**:95, 1902.
31. *Idem:* The treatment of trachoma by the x-rays. Tr. Ophth. Soc. U. Kingdom **23**:10-23, 1903.
32. Meldolesi, G., and Sabbadini, D.: Sulla terapia del tracoma con le radiazioni secondarie ottenute col metode del Ghilarducci. Radiol. med. **10**:222, 1923.
33. Merritt, E. A., and McPeak, F. M.: Roentgen irradiation in unresolved pneumonia. Am. J. Roentgenol. **23**:45-48, 1930.
34. Musser, J. H., and Edsall, D. L.: A study of metabolism in leukemia, under the influence of the x-ray, with a consideration of the manner of action of the x-ray and of some precautions desirable in its therapeutic use. Tr. A. Am. Physicians **20**:294-323, 1905.
35. Pusey, W. A.: Lupus healed with roentgen rays: report of case. J. A. M. A. **35**:1476-1478, 1900.
36. Quimby, A. J., and Quimby, W. A.: Unresolved pneumonia; successful treatment by röntgen ray. New York Med. J. **103**:681-683, 1916.
37. Rankin, F. W., and Palmer, B. M.: Postoperative parotiditis; treatment without and with radium. Ann. Surg. **92**:1007-1013, 1930.
38. Rudis-Jicinsky, J.: Lupus treated by x-rays. Am. X-ray J. **3**:423, 1898.
39. Stephenson, S., and Walsh, D.: Short note on the cure of trachoma by x-ray tube exposure and by high-frequency brush discharges. Lancet **1**:237, 1903.
40. Thielemann, R.: Zur Wirkungsweise des Radiumbestrahlung auf die trachomatöse Bindehaut. Ztschr. f. Augenh. **14**:559-569, 1905.
41. Torrey, R. G.: Roentgenotherapy in disorders of the respiratory tract, particularly those associated with enlargement or persistence of the thymus gland, and those associated with unresolved pneumonic exudates. S. Clin. North America **7**:221-235, 1927.
42. Tsuzuki, M.: Experimental studies on the biological action of hard roentgen rays. Am. J. Roentgenol. **16**:134-150, 1926.
43. Warthin, A. S.: An experimental study of the effects of roentgen rays upon the blood-forming organs, with special reference to the treatment of leukemia. Internat. Clin. **4**:243-277, 1906.
44. Williams, F. H.: *The roentgen rays in medicine and surgery as an aid in diagnosis and as a therapeutic agent; designed for the use of practitioners and students.* Third edition. 757 pp. New York: Macmillan Co., 1903.

Discussion

Dr. Benjamin Parvey, Boston: I should like to ask Dr. Desjardins if he can tell us anything about the treatment of pilonidal sinus by x-ray.

Dr. Herman A. Osgood, Boston: I should like to ask Dr. Desjardins whether sulfanilamide should be administered simultaneously with x-ray in acute infections. There are so many new conditions that Dr. Desjardins has brought up from the standpoint of x-ray treatment — that is, conditions new to us — that there should be a considerable field for discussion. Perhaps Dr. Desjardins will add a little more detail as to the treatment of pneumonia, about which we have heard a good deal.

A MEMBER: Can Dr. Desjardins tell us anything about the treatment of phlebitis?

DR. DESJARDINS: I am glad the question about phlebitis was brought up. We have treated quite a number of cases of acute phlebitis. Some of them do very well; in fact a majority do well; but here again it is very important to treat widely. If, for instance, the phlebitis affects a lower extremity, the entire extremity and portions of the lower part of the trunk should be treated. Trying to treat only a patch on the leg where the condition is worst is not likely to yield the best result. When phlebitis is treated early, as soon as the diagnosis is made, it is surprising how well this kind of inflammation responds. On the other hand, if treatment is started late, the results are not so gratifying.

As for the possible advantage of combining sulfanilamide with roentgen ray treatment, this new group of drugs has put an entirely different face on the treatment of certain infections, and this must be taken into account. What I have said about roentgen ray treatment was based on work done before the days of sulfanilamide. There is no question that some of these drugs have effects which are so striking that there is no dodging our responsibility to make use of them, and in certain cases I should not take the position that roentgen rays should be utilized to the exclusion of sulfanilamide or similar drugs. We should employ every remedy available, and if the condition yields as well to sulfanilamide, by all means it should be used and continued until the case is cured. On the other hand, if a case does not respond well to sulfanilamide, or the response is not so good as one would expect, I should not hesitate to use roentgen rays also. In pneumonia, if roentgen rays are to be employed at all, they should be used as soon as the diagnosis is made. To postpone their use until later is to rob them of part or all of their possible efficacy.

I have had no experience with the treatment of pilonidal sinus with roentgen rays, although I am aware that reports of good results have been published in the literature. I have not had a single case in which to test this method, and without having had an opportunity to try it in fifty or a hundred cases I should not venture to express an opinion.

SULFANILAMIDE IN THE TREATMENT OF ERYSIPELAS*

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FOLLOWING the introduction of sulfanilamide as a chemotherapeutic agent in the treatment of hemolytic-streptococcus infections, reports have appeared describing its use in the therapy of erysipelas. It has seemed worth while to review this material and to present the data from cases treated at the Boston City Hospital in which the drug has been administered.

The disease, characterized by a red, spreading, indurated lesion of the skin, most frequently involving the face and often complicating operative wounds, has been shown to be caused by streptococci which are immunologically and culturally members of Lancefield's Group A, but of no particular serological type.[1] The organisms can usually be recovered from the local lesions, where they have been found histologically to be confined to the lymphatics and to spread through them.

The facial type is frequently preceded by either acute or chronic upper respiratory infection, and in these cases the organisms can regularly be recovered from the nose, from which they have been transferred to the surrounding skin, invading it through minute excoriations. The onset is most often acute and frequently accompanied by chills, and is followed in one to three days by the appearance of the skin lesion, the diagnosis being delayed until the third day in as many as 30 per cent of cases, owing to the late appearance of the lesion.[2] Only a very few cases are afebrile, high fever persisting for four to ten days being the rule. Fall of temperature is by lysis or crisis, frequently the latter, and occurs oftenest on the sixth to eighth day, in an average of 7.9 days.[2] The clearing of the skin lesion lags behind this event for several days. The mortality rate varies with the age of the patient and with the presence of chronic debilitating disease. Below the age of two, 50 to 75 per cent of all patients may be expected to die, and beyond the fifth decade there is a sharp rise in the percentage of fatal cases. Between these two groups the death rate is less than 5 per cent. Seegal and Seegal[2] have pointed out that in 85 per cent of their fatal cases there was some underlying disease of a serious nature, and Keefer and Spink,[3] at the Boston City Hospital, found that in 80 of 220 fatal cases there was some such condition. The presence of a blood culture positive for the hemolytic streptococcus is of grave prognostic significance. Nearly all the infants in whom this sign has been positive have died.

Complications in the course of the disease other than local abscess, cellulitis or necrosis of the skin are uncommon, but bronchopneumonia, nephritis and meningitis occur.

Recurrence of attacks similar to the first occur after varying time intervals in many individuals, and some patients seem to become permanently

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more susceptible. Some cases have a relapse ten to twenty days after the onset of the disease, when recovery seems to be firmly established. Patients displaying this phenomenon have been shown to be divisible into two groups; those who have organisms demonstrable at the local lesion, in many cases with a high titer of circulating antibody, and those who have no demonstrable organisms but react to bacterial products, presumably on the basis of local hypersensitivity of an allergic nature.[4]

Of the many articles in the literature discussing the use of sulfanilamide in the therapy of erysipelas, the following are the most significant.

Peters and Havard[5] have treated 47 cases with sulfanilamide, in all of which the spread of the lesions was arrested within twenty-four hours and the temperature returned to normal within forty-eight hours. No other details or control series are mentioned.

Snodgrass and Anderson[6] present a detailed study of 106 cases treated with Prontosil and a control group in which ultra-violet light was used alone. No spread of the lesions was observed after twenty-four hours in 82 per cent of the drug-treated cases, whereas this result was achieved in only 59 per cent of the controls in the same time. In 76 per cent of the former the temperature was normal within forty-eight hours; this occurred in only 48 per cent of the latter. Recurrences, complications and deaths were of the same order of magnitude in both groups.

Hageman and Blake[7] administered sulfanilamide to 27 patients and compared the results with a similar number studied the year before in the same hospital. The febrile duration of the disease was 13.9 days in the control and 5.3 in the treated series, recovery in the latter occurring on an average 2.2 days from the onset of therapy. Two infants under ten days of age with positive blood cultures recovered. The usual dose was 4 or 5 gm. per day. Infectious complications occurred in 3 cases and recurrence in 1. Of 3 deaths, none seemed directly attributable either to the infection or to the sulfanilamide.

Meyer-Heine and Hugenin[8] regard the drug as a specific therapeutic agent in this disease, its exhibition by mouth being followed in 148 of 150 cases by a rapid fall in temperature and subsidence of the local lesion within forty-eight hours. There were no deaths, but local complications occurred in a number of cases. Bloch-Michel et al.[9] have had a similar experience in 180 cases, except that there were 7 deaths, all of aged and debilitated patients. A dose of approximately 2 gm. per day was used in both these investigations.

The temperature and pulse in 23 cases treated by Kramer[10] became normal in an average of 4.3 days against an average of 11.3 days for a comparable control group. The dosage was believed to be inadequate in the 2 cases which failed to respond to treatment. Eighteen of 22 cases followed by Frankl[11] showed a critical fall in temperature in the first or second twenty-four hours and the patients were fever-free within three days. Spread of the local lesion after forty-eight hours was observed in only 2 cases. Complications were present in all cases with prolonged fever; 1 death was noted, that of an old and debilitated man.

Breen and Taylor[12] administered 2 gm. of sulfanilamide daily in a series of 35 cases of erysipelas and found that 33 regressed, with a return of the temperature to normal within forty-eight hours. There were 2 deaths, one of a patient who entered the hospital in a moribund state, and the other as the result of a cardiovascular accident.

Nelson, Rinzler and Kelsey[13] treated 344 patients suffering from erysipelas with sulfanilamide and compared the results with those obtained by various other methods in over 4000 cases. The hospital stay was found to have been shortened from 11.0 to 7.0 days, the duration of fever from 6.8 to 4.2 days and the mortality rate from 8.0 to 1.5 per cent. In children the mortality rate was reduced from 19.7 to 12.9 per cent.

ANALYSIS OF CASES

We have studied without special selection all those patients admitted to the male wards with a diagnosis of facial erysipelas from October, 1937, to June, 1939—42 in all. As a control, the records of 43 similar patients admitted during 1936 and 1937 before the use of sulfanilamide was instituted have been evaluated. All received a standard therapy consisting of bed rest, fluids, sedatives and cold magnesium sulfate compresses on the affected areas. Those to whom sulfanilamide was administered received as a routine 6 or 8 gm. by mouth in the first twenty-four hours, with a maintenance dose of 3 to 5 gm. per day thereafter.

In so far as various factors existed which might influence the course of the disease, the two groups were roughly comparable. Advanced age has been shown to predispose to the severity of the infection;[3] 50 per cent of the treated and 48 per cent of the control cases were in the fifth, sixth or seventh decade. Since debilitating disease also tends to modify the course of the disease unfavorably, the cases were examined in order to determine its presence. Fourteen, or 33 per cent, of the controls were found to be suffering from serious chronic disease. These were predominantly chronic alcoholism, marked generalized and cere-

bral arteriosclerosis, congestive heart failure and rheumatic heart disease; there was 1 case of diabetes mellitus. In the treated group 13 patients, or 30 per cent, were found to have similar conditions; chronic alcoholism or cirrhosis of the liver occurred in 8, and fibroid pulmonary tuberculosis, luetic heart disease, chronic osteomyelitis of the hip, postencephalitic Parkinson's disease and rheumatoid arthritis each in 1 case. The blood cultures of all patients were negative when this examination was made, except for 1 case in the controls which was positive for a hemolytic streptococcus and 2 cases in the treated group, one positive for *Staphylococcus aureus,* and the other for a hemolytic streptococcus; all patients with positive cultures died.

As criteria for the evaluation of the effect of the drug, we have considered the duration of fever, the incidence of complications and the mortality. It has proved impossible to use the subsidence of the skin lesions as such a measure because of insufficient data in the untreated cases.

The duration of fever from the onset of illness in the control group averaged 7.5 days, as compared with 7.1 in the treated cases, the former having extremes of four and twenty-three days, the latter of two and nineteen days. After the beginning of sulfanilamide therapy 8 patients were afebrile within twenty-four hours, 13 within forty-eight, 6 within seventy-two and 12 after seventy-two. If the time of institution of therapy is considered in relation to the onset of the disease, it is found that of 21 patients treated on or before the third day of illness the total febrile course averaged 5.2 days, with an average of 3.0 days after beginning the drug. In cases in which the drug was given after the third day, fever persisted for an average of 9.1 days and subsided in an average of 4.2 days after the onset of medication.

The total duration of fever was therefore markedly shortened in those patients treated on or before the third day of the illness. In those treated after this interval the average febrile period was longer than in the control group. The course of the illness in these individuals was more severe, and an average of twenty-four hours more elapsed before the temperature reached normal after exhibition of the drug. Fever continued for more than ten days in 7 of the latter patients, and in only 2 of those treated early.

Complications were present in 7 of the untreated patients and 9 of the treated. Of the former, 3, or 7 per cent, had a recurrence; a similar number had abscess of the face; 1 had bronchopneumonia, and 1, acute purulent otitis media. Of the latter group, 2, or 5 per cent, suffered recurrence; 4, or 10 per cent, developed abscess of the face; 1 had a toxic hepatitis, and 1, bronchopneumonia.

It is therefore impossible to demonstrate any important difference in the complication rate between the two groups. Of those patients who received sulfanilamide early in the course of the disease, suppurative complication occurred in only 1 (abscess of the eyelid), but 2 suffered relapse.

There was 1 death in the untreated series, a mortality rate of 2 per cent, distinctly lower than the 16 per cent previously reported from this hospital.[14] Three deaths occurred among the treated cases, a rate of 7 per cent. These cases require special comment.

Case 1. A 73-year-old man, admitted to the hospital with a 2-day history of swelling of the face, was found to suffer from typical facial erysipelas complicated by arteriosclerotic heart disease, with auricular fibrillation and chronic pulmonary fibrosis of unknown etiology. The temperature was 100°F., and the pulse 80. Sulfanilamide was immediately exhibited by mouth and 6 gm. was given in the first 12 hours. In spite of this treatment, the giving of digitalis, and the usual supportive therapy, the patient became irrational, the temperature rose to 105°F., and death occurred 24 hours after entry. A blood culture was positive for a hemolytic streptococcus.

Case 2. A 32-year-old man was admitted to the hospital with a history of coryza and sore throat of 3 days' duration and swelling of the face for 24 hours. He had had two previous admissions to the hospital because of marked cardiac failure due to rheumatic heart disease with mitral stenosis. He was found to have the lesions of facial erysipelas and the signs of cardiac enlargement and mitral stenosis without decompensation. The temperature was 100°F., and the pulse 90. The blood culture was sterile. Six grams of sulfanilamide was administered in the first 24 hours, but pulmonary edema ensued and the patient died 24 hours later in acute peripheral vascular collapse.

Case 3. A 42-year-old man was admitted to the hospital with a history of swelling of the face for 6 days following a cold. He had used large amounts of alcohol over a long period of time. He was found to be suffering from extensive erysipelas involving the face, scalp and neck. A blood culture was positive for *Staphylococcus aureus.* The temperature was 104°F., and the pulse 100. The oral administration of sulfanilamide was begun in doses of 2 gm. every 6 hours, but after 4 gm. had been given the patient developed profound peripheral vascular collapse and died.

These cases are presented in order to illustrate that certain individuals suffering from changes of old age, arteriosclerosis, heart disease, chronic alcoholism or some other debilitating disease will continue to die as the result of an acute infectious process, such as erysipelas, even though sulfanilamide be exhibited as soon as the patient comes under the care of the physician. It is important

to point out that one of these patients was treated on the second and one on the third day of his illness. It cannot, therefore, be said that early treatment leads in every case to a satisfactory termination of this disease. The third patient, treated first on the seventh day, with a complicating *Staphylococcus aureus* septicemia, could not have been expected to recover.

Few untoward side effects were observed as the result of the use of sulfanilamide except cyanosis and headaches. Anemia and agranulocytosis did not occur, but dermatitis was observed in 1 case, and several of the more prolonged fevers may have been due to the presence of this drug in the body of the patient.

DISCUSSION

The mode of action of sulfanilamide and its relation to recovery in erysipelas require comment. Although the exact immunologic processes involved in recovery in this disease have never been fully elucidated, the work of various investigators has in part clarified the picture. Birkhaug[15] has reported a circulating soluble toxin obtained from the hemolytic streptococcus, and believes that development of antitoxin in the blood must precede the recovery process, a thesis which Francis[16] was unable to confirm. The latter postulates the development of allergy to bacterial products, followed by the appearance of an antiallergin as a prerequisite to the recovery state. Local tissue immunity of the skin has been suggested and in part demonstrated experimentally by Gay and Rhodes[17] and Rivers and Tillett,[18] but has not been demonstrated in the infected human subject. Spink and Keefer[4] were able to demonstrate the presence of immune bodies against the hemolytic streptococcus in the form of antistreptolysin, antifibrinolysin and increased bactericidal power of whole blood for this organism. In some cases these were present in marked degree when the patients were first seen, but in others they were observed to increase in amount during the disease and to fall away after recovery had taken place. In certain cases with recurrence, organisms could not be demonstrated in the local lesions, but typical attacks could be induced by the subcutaneous injection of toxic filtrates of the organism, suggesting that the reaction was one of response of sensitized tissues to bacterial products.

In the light of the above studies, it seems fair to conclude that antibacterial and perhaps antitoxic antibodies, both humoral and of the local tissues, and local sensitivity of an allergic nature all play a role in the recovery from the disease, and that the latter event does not occur until some of these products have reached a high level which is maintained long enough to sterilize the local lesion.

The mode of action of sulfanilamide has been repeatedly shown to be that of bacteriostasis, with almost no bactericidal effect in various media in vitro. We[3] have shown that this is also true of whole blood, and the data suggest that the drug possesses increased effect in bloods with a high antistreptococcus antibody titer. It has also been shown by Colebrook et al.,[19] Long and Bliss[20] and us[14] that in mouse protection tests the animals survive only so long as the drug is present in adequate concentration, and that after its withdrawal most of the animals succumb, presumably because they have failed to develop any natural immunity against the organism, which has been inhibited but not killed by the drug.

From these observations it would seem that sulfanilamide cannot be expected to effect immediate cures of erysipelas. It should be expected that it will slow the rate of multiplication of the organism, and thus prevent some of the destructive local effects and decrease the rate of spread through the lymphatics, but a fall in temperature and subsidence of the local lesion must presumably await the development of antistreptococcus immune bodies in the afflicted individual. That this is so is indicated by the previously recorded data, since a fall in temperature has rarely occurred in less than forty-eight hours after the administration of the drug by mouth, and the average course in the group treated early has been about five days. Neither should sulfanilamide be expected to prevent that type of relapse with sterile local lesion and hypersensitivity to bacterial products, since no action affecting this kind of reaction has been demonstrated.

It is difficult to draw any definite conclusions from the above observations as to the efficacy of sulfanilamide in the treatment of erysipelas. The previously published data are, on the whole, insufficient and without controls, but all authors have believed that the drug was a useful adjunct in the treatment of this condition.

The data presented in this paper suggest that the duration of the disease is shortened markedly when the drug is given on or before the third day of the illness. Clinically these patients have a mild disease and a short convalescence. After the third day it has been impossible to demonstrate any effect of this agent on the course of erysipelas. This is to be expected, because by the fourth day the local lesions are usually fully developed and relief by the natural mechanisms of the body must be awaited. In cases treated early the circumstances are different, as the infection is still spreading through the skin, and

it may be possible to curtail markedly the area involved in the local lesions as well as the toxemia by the use of sulfanilamide, thus mitigating the severity of the disease and limiting its extent and duration.

No difference in the complication rate has been demonstrated by this or any previously reported study, and the incidence of death is so low as to be an unreliable approach in the case of adults. The fact that infants under six months of age with blood cultures positive for the hemolytic streptococcus have recovered is encouraging, and suggests the efficacy of the drug against this organism.

On the whole, the therapeutic results of the use of sulfanilamide in facial erysipelas seem sufficiently encouraging to continue its routine use in the treatment of this disease, with emphasis placed on its administration in adequate dosage as early as possible after the onset of the illness.

SUMMARY AND CONCLUSIONS

The effect of sulfanilamide on the course of facial erysipelas has been studied in 42 cases and compared with 43 similar cases treated previously.

The drug is found to shorten the course of the illness and to decrease its extent and severity if it is administered before the third day of the disease. It has little effect after this interval.

Complications occur frequently in the treated cases, but less often in those treated early.

Recurrences and relapses occur among the treated cases as often as among the untreated group.

Death occurs in certain aged or chronically ill patients even though sulfanilamide is administered early and in adequate doses.

REFERENCES

1. Keefer, C. S., and Spink, W. W.: Studies of hemolytic streptococcal infection. III. The characteristics of hemolytic streptococci isolated from patients with erysipelas. J. Clin. Investigation **16**:155-159, 1937.
2. Seegal, D., and Seegal, B. C.: Facial erysipelas: a study of 281 cases treated at the Massachusetts General Hospital from 1870 to 1927. J. A. M. A. **93**:430-436, 1929.
3. Keefer, C. S., and Spink, W. W.: Studies of hemolytic streptococcal infection. I. Factors influencing the outcome of erysipelas. J. Clin. Investigation **15**:17-19, 1936.
4. Spink, W. W., and Keefer, C. S.: Studies of hemolytic streptococcal infection. II. The serological reactions of blood during erysipelas. J. Clin. Investigation **15**:21-35, 1936.
5. Peters, B. A., and Havard, R. V.: Chemotherapy of streptococcal infections with *p*-benzylamino-benzene-sulphonamide. Lancet **1**:1273, 1937.
6. Snodgrass, W. R., and Anderson, T.: Prontosil in the treatment of erysipelas; controlled series of 312 cases. Brit. M. J. **2**:101-104, 1937.
7. Hageman, P. O., and Blake, F. G.: Clinical experience with sulfanilamide in the treatment of beta hemolytic streptococcic infections. Am. J. M. Sc. **195**:163-175, 1938.
8. Meyer-Heine, A., and Hugenin, P.: Traitement de l'érysipèle par le chlorhydrate de sulfamido-chrysoidine. Presse méd. **44**:454-457, 1936.
9. Bloch-Michel, H.; Conte, M., and Durel, P.: L'emploie des dérivés sulfamidés non azoiques dans le traitement de l'érysipèle. Presse méd. **44**:1583, 1936.
10. Kramer, W.: Ueber Erfahrungen bei der Erysipelbehandlung mit Prontosil. München, med. Wchnschr. **83**:608-610, 1936.
11. Frankl, J.: Ueber den Wert des Prontosil in der Therapie des Erysipels. Klin. Wchnschr. **15**:1563-1567, 1936.
12. Breen, G. E., and Taylor, I.: Erysipelas treated with prontosil. Lancet **1**:1334-1336, 1937.
13. Nelson, J.; Rinzler, H., and Kelsey, M. P.: Sulfanilamide treatment of erysipelas. J. A. M. A. **112**:1044, 1939.
14. Keefer, C. S., and Rantz, L. A.: Sulfanilamide: a study of its mode of action on hemolytic streptococci. Arch. Int. Med. **63**:957-973, 1939.
15. Birkhaug, K. E.: Erysipelas. VIII. Bacterial allergy to Streptococcus erysipelatis in recurrent erysipelas. J. A. M. A. **90**:1997-2001, 1928.
16. Francis, T., Jr.: Studies on pathogenesis and recovery in erysipelas. J. Clin. Investigation **6**:221-236, 1928.
17. Gay, F. P., and Rhodes, B.: Experimental erysipelas: studies in streptococcus infection and immunity. IV. J. Infect. Dis. **31**:101-115, 1922.
18. Rivers, T. M., and Tillett, W. S.: Local passive immunity in the skin of rabbits to infection with (1) a filterable virus and (2) hemolytic streptococci. J. Exper. Med. **41**:185-194, 1925.
19. Colebrook, L.; Buttle, G. A. H., and O'Meara, R. A. Q.: The mode of action of *p*-aminobenzenesulphonamide and prontosil in haemolytic streptococcal infections. Lancet **2**:1323-1326, 1936.
20. Long, P. H., and Bliss, E. A.: Para-amino-benzene sulfonamide and its derivatives; experimental and clinical observations on their use in the treatment of beta-hemolytic streptococcic infections: preliminary report. J. A. M. A. **108**:32-37, 1937.

SUPPRESSION OF URINE COMPLICATING PYELOGRAPHY*

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THE development of the newer synthetic organic compounds containing iodine has furnished the urological and roentgenological armamentarium with pyelographic materials of great value. By their use, injected either intravenously or through a catheter passed into the ureter, excellent, highly informative shadow outlines of the urinary tract are obtained in the x-ray film. The use of the intravenous method of injection has become especially widespread, for by this means it is often possible to avoid the discomfort attending the use of the cystoscope.

The materials generally used today for excretory pyelography are Skiodan (sodium monoiodo-methane sulfonate), Diodrast, also called Neo-skiodan or Iopracyl (3, 5-*di*iodo-4-pyridone-*N*-acetic acid dissolved with diethanolamine), and Hippuran (sodium ortho-iodo-hippurate). Each of these organic iodine compounds is opaque to x-rays, and after intravenous injection appears quickly and in high concentration in the urine. Experimentally, and in clinical use as well, each is found to be treated by the body as an inert foreign material which is for the most part quickly excreted unchanged by way of the urine. The iodine, though large in amount, is firmly bound. On theoretical grounds the union of the iodine atom with hippuric acid, which itself is a normal product of metabolism, would seem to furnish a substance more apt to be well tolerated by the body than when the iodine is united with more complex forms. In clinical use, however, no demonstrable superiority of any one of these substances over the other has been experienced.

Recently, Diodrast and Hippuran have been studied by physiologists with regard to their passage through the kidney.[1-4] It is found that these substances are promptly taken out of the blood stream by the renal tubules, to appear in high concentration in the tubular urine. The suggestion follows that by their use it may be possible to measure renal blood flow, and at the same time to differentiate tubular function and that of the glomerulus.

In view of the very appreciable amount of work thrown on the cells of the renal tubules by the injection of these foreign pyelographic substances into the blood stream, it might be expected that untoward effects would be noted occasionally, especially in cases where the kidney tissue was the site of previous disease. But such accounts appear very rarely indeed in the literature.

In 1936 Cumming and Chittenden[5] studied the subject of intravenous and retrograde urography by means of a questionnaire. They report the following unfavorable or "allergic" reactions to the intravenous injection: urticaria, rhinitis, lacrimation, salivation and edema of the glottis. Many of these manifestations are those seen in the state of iodism after the administration of some such drug as potassium iodide. Here the effects may be of toxic origin caused by the drug itself, but since many patients can take iodides for long periods without showing unfavorable reactions, whereas some respond by a severe coryza after only twenty-four hours, it is likely that here too allergy may play a part. In Cumming and Chittenden's report, a few cases of slight transient anuria following intravenous injection are noted, without further comment.

As concerns the retrograde injection of pyelographic media into the renal pelvis, the earlier literature contains an occasional report of a death seemingly so caused. We are unable to find any such reports when Skiodan, Diodrast or Hippuran was used. It is to be noted in this regard that there is always some absorption from the renal pelvis into the blood stream of whatever substance is injected into it through the ureteral catheter. It has been shown also that this retrograde absorption, the so-called pyelovenous or pyelolymphatic reflux, takes place without there being caused any significant increase of the intrapelvic pressure at the time of injection. An interesting illustration of this fact has lately been seen by us after pelvic injection of a solution of the maltoside of sulfanilamide in order to combat renal infection in patients who were unable, for one reason or another, to take the drug by mouth. In such cases we were able to demonstrate sulfanilamide in the blood stream in appreciable amounts shortly after injection.[6] Further, at operation on a kidney free from infection, of which a pyelogram has been made by retrograde injection the day previously, one frequently notes an edema of moderate amount involving the fatty tissue immediately surrounding the renal pelvis. In the absence of other probable explanation such circulatory interference has always been thought by us to be a result of the recent intrapelvic injection.

From all evidence at hand, therefore, it is probably fair to assume that a portion of whatever

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is injected into a renal pelvis will reach the blood stream.

It is doubtless true that any substance, however innocuous, used for pyelography places a burden on the kidney. When the substance is used in the form of intravenous and retrograde injections at the same time, or in the presence of a diminished renal excretory power, as when the function of one kidney is temporarily suspended, serious embarrassment of renal function may follow. The following cases are in point.

Case 1 (No. 48863). A 53-year-old man suffered an attack of sharp pain in the region of the left groin which persisted intermittently for 2 days. Three years before this he had had treatment for a duodenal ulcer, which was continued in the form of alkalies and diet during the following 2 years. The suggestion that the present attacks of pain were due to a urinary calculus formed under this regime was considered likely.

Examination showed that the urine contained a few red and white blood cells, and a large amount of crystalline material in the form of triple phosphates. X-ray films failed to reveal any shadow suggestive of calculus, but urine delivered through a ureteral catheter on the right side showed a few white blood cells, while that from a catheter on the left contained blood. The course of the ureteral catheters as seen in the x-ray film, together with the presence of a soft-tissue shadow, suggested to the roentgenologist the possibility of a horseshoe kidney. Following this examination the daily output of urine was of normal amount. Two days later, it being found impossible to pass a catheter up either ureter because of edema of its orifice, an intravenous injection of 20 cc. of Diodrast was made. No excretion of this material into either renal pelvis occurred, and during the following 2½ days no urine was formed. The patient perspired freely, complained of discomfort in the lower portion of the abdomen and became increasingly drowsy. Forty-eight hours later he began to vomit. The nonprotein nitrogen of the blood measured 73 mg. per 100 cc. at this time, and later reached 112 mg. Under active treatment by enemas, hot packs and intravenous saline solution containing glucose, renal secretion began again after a cessation of nearly 3 days. Subsequent tests of renal function showed a prompt return to normal, so that at the end of 2 weeks the patient was able to return home apparently well in every respect.

The condition of the kidneys was investigated 4 months after the above episode and again 2 years later. Normal urea clearance and normal amounts of nonprotein nitrogen in the blood were found.

Case 2 (No. 57693). A 57-year-old man was seen 3 hours after the onset of an attack of colic and pain in the left flank, accompanied by dysuria and urgent urination. The left kidney appeared to be slightly enlarged, its lower pole being easily palpable but non-tender. The urinary sediment showed many red blood cells. The nonprotein nitrogen of the blood was 26 mg. per 100 cc. A presumptive diagnosis of left-sided renal colic due to calculus was made and the patient was put to bed and given sedatives. Urological investigation the following day found the left ureter patent as far as the renal pelvis. The urine from the left kidney contained red blood cells, but no pus or bacteria. X-ray films showed a small, poorly visible shadow at the tip of the ureteral catheter in the renal pelvis. Six cubic centimeters of a solution of Hippuran was used in order to make a retrograde pyelogram. Examination of this showed a somewhat irregular outline of the renal pelvis. No uncomfortable reaction followed the pyelography, and the next day excretory urograms were made so as to get a comparative film of the pelvic abnormality. The outline of the right renal pelvis 5 minutes after injection was well visualized and was normal. There was delayed excretion and poor concentration of the opaque medium from the left kidney, making visualization of the calices and pelvis unsatisfactory. Immediately after intravenous urography the patient passed about 25 cc. of blood-tinged urine, but after this passed no urine for 74 hours. He gradually grew more drowsy and had a sensation of tension or fullness in each flank. During 48 hours he was able to take some fluid by mouth, but during the 3rd day he vomited. There was no pulmonary or peripheral edema, but the temperature was as high as 101°F. He received over 5000 cc. of fluid each day, mostly in the form of saline solution containing 5 per cent glucose. During the 3rd day he was also given 100 cc. of a hypertonic (10 per cent) solution of sodium chloride intravenously. The nonprotein nitrogen of the blood reached a level of 96 mg. per 100 cc. At the end of the 3rd day 30 cc. of bloody urine was passed, followed an hour later by 75 cc.; and during the next 18 hours there was passed over 6000 cc. of urine, which contained less blood on each urination. A day later the urinary sediment showed both white and red blood cells in moderate number, and an occasional granular cast. Two days after the kidneys had begun to act again they were found to excrete 70 per cent of a solution of phenolsulfonephthalein in the 1st hour and 20 per cent in the 2nd. A concentration test showed a maximum specific gravity of 1.020 and a minimum of 1.010. Nine days later a divided functional test of the kidneys through the ureteral catheters showed excretion values of 13 per cent phenosulfonephthalein from the right kidney and 17 per cent from the left in a 10-minute period. The urine still contained a slight trace of albumin. After returning home this patient was investigated by his physician for evidences of nephritis, but none were present. A year after the above episode he was again seen by us. He reported excellent health in the meantime, and the urine was normal.

Case 3 (No. 60326). A 35-year-old man came to the Emergency Ward complaining of steady pain in the right flank during the previous day. There had been no colic. Examination showed a temperature of 100°F. and a white-cell count of 14,000. The region of the appendix was not remarkable, but slight tenderness was present in the right costovertebral angle. The urine contained red blood cells in small numbers and an occasional white cell. A plain x-ray film of the urinary tract failed to show any shadow suggestive of stone. Six hours later, the temperature having risen to 101°F., the patient was admitted to the hospital for observation. Twelve hours later the temperature had returned to normal, but the white-cell count was still elevated. There was continued pain in the right side. Intravenous pyelography with 20 cc. of Diodrast gave urograms in which the left kidney pelvis was outlined promptly and appeared normal. For as long as 30 minutes after injection no shadow appeared on the right side, there being no excretion. Although nothing suggesting the shadow of a calculus could be seen, it was thought that the patient's ailment probably lay in a right ureteral calculus, blocking the kidney and transparent to x-ray. A cystoscope was therefore passed and the right ureter was catheterized. The efflux was noted to contain blood before the catheter was inserted. About 3 cm. above the bladder a partial obstruction was encountered, after the passing of which a profuse flow of urine was obtained through the catheter. Beyond this point no further im-

pediment was found as far as the renal pelvis. Exploration of the left ureter revealed no abnormality. A divided function test with phenosulfonephthalein showed each kidney to be normal in its excretory power. A retrograde injection of 5 cc. of Hippuran was made into the right renal pelvis, and stereoscopic x-ray films were taken. These showed the right renal pelvis of normal size and contour. The faint shadow of a calculus was present in the lower third of the ureter; the stone apparently lay adjacent to the catheter and at or somewhat above the point at which the passage of the catheter had encountered resistance.

On the theory that relief of obstruction of the right kidney was indicated, the ureteral catheter was allowed to remain in place. It was removed, however, after 2 hours because, although its lumen was patent, no urine flowed through it. At this time the patient passed about 50 cc. of somewhat bloody urine from the bladder, but did not void again for 76 hours. His course during this time was stormy. Besides the presence of distention, nausea and vomiting, the white blood cells were markedly increased in number, there were several chills followed by high fever and a culture of the blood showed the presence of *Staphylococcus albus*. Nevertheless the kidneys eventually responded to forced intravenous fluids together with enemas, so that on the day following the period of anuria 2500 cc. of urine was passed.

During the next 5 days large amounts of urine were passed, but the temperature remained elevated. The patient's appearance had improved, but there was still considerable tenderness over the right kidney. The right ureter was therefore re-examined by catheter. The area of obstruction was again encountered, and the urine from the right kidney showed considerable pus and *Staphylococcus albus*. The left kidney seemed to have normal function and to secrete a sterile urine. On the 14th hospital day the patient was subjected to operation, at which a thickened, scarred area in the ureter was found 3 cm. above the great vessels. This area was 2 cm. long, and around it the periureteral tissues showed distinct adhesions and induration. Incision demonstrated an inflammatory stricture; no stone was present. The stricture was dilated to No. 12 French, and drainage was instituted. Convalescence was uneventful, but the obtaining of a positive culture for *Bacillus coli* from the urine made necessary a subsequent course of sulfanilamide. The patient recovered but has continued under observation in the ambulatory clinic. No doubt further dilatation of the ureteral stricture will be necessary.

Case 4. A somewhat obese man of 48 underwent cystoscopic examination in a neighboring city to determine the cause of an intermittent though marked hematuria, first noted 3 weeks earlier. Previously he had been entirely well. A papillary growth of considerable size was found overlying and obscuring the right ureteral orifice. A retrograde pyelogram of the left renal pelvis was made, using Skiodan. Since a similar evaluation of the right renal pelvis was impossible, the usual amount of a solution of Diodrast was injected into a vein of the arm. X-ray films obtained by these means showed a normal renal pelvis of the left kidney in both the retrograde and excretory urograms. The right pelvis failed to fill, and so was not visible in any of the films made after intravenous injection. It was therefore concluded that the hematuria was due to a papillary carcinoma of the bladder involving the right ureteral orifice and causing loss of renal function in the kidney above. The left urinary tract and kidney were normal.

Following these examinations increasing distention of the abdomen, vomiting and gradual suppression of urine occurred. The patient was seen in consultation 3 days later. At this time the bladder was still empty, in spite of the previous administration of mercurial diuretics and one small intravenous injection of saline solution containing 5 per cent glucose. The sensorium was not clouded, there was only moderate fever and the pulse was of good quality, although somewhat elevated. A Wangensteen tube which had been adjusted so as to control vomiting could not be tolerated. No evidence of edema was seen, and palpation of either kidney was made impossible by soft distention of the abdomen.

Advice was given to omit all mercurial diuretics and to force fluid in the form of intravenous injections of saline solution in 500-cc. amounts up to 5000 cc. daily, the first injection to contain 10 per cent glucose and the others 5 per cent. Under this regime the urinary suppression ceased after a day; at the end of 36 hours urine was being secreted copiously and the patient's general condition was again normal.

DISCUSSION AND CONCLUSIONS

It is to be noted that in each of these cases injections of urographic mediums were made by both the intravenous and retrograde methods. The injections followed each other immediately in 2 cases, and within twenty-four hours and forty-eight hours respectively in the others. Complete cessation of urine occurred immediately after the second injection. After anuria for various periods, seventy-six hours in the most marked case, the kidneys resumed their function, having been stimulated in the meantime by copious injections of saline solution containing glucose. In only 1 case was there evidence of infection. Before investigation each of the patients presented either partial or complete inhibition of the function of one kidney; in 3 cases this was caused by the passage of a small calculus, and in 1 by a neoplasm of the bladder. The unobstructed kidney was apparently normal at this time. In 3 cases subsequent study of the kidneys at various times following the occurrence of the period of anuria demonstrated no evidence of nephritis.

It is evident that suppression of urine of severe and alarming degree may follow the injection of the usually innocuous pyelographic mediums when these are used in an amount too large to be passed successfully through a normal single kidney. No signs of toxicity occurred in the series other than those due to the cessation of renal function.

In the light of these experiences it seems wise in cases of unilateral or bilateral reduction of normal renal function to repeat pyelographic studies, especially by both the excretory and retrograde methods, only after a forty-eight-hour interval.

REFERENCES

1. Smith, H. W.: *The Physiology of the Kidney*. 310 pp. New York: Oxford University Press, 1937. P. 196.
2. *Idem*: New aspects of renal physiology. J. Urol. **41**:867-876, 1939.
3. Elsom, K. A.; Bott, P. A., and Shiels, E. H.: On the excretion of skiodan, diodrast, and hippuran by the dog. Am. J. Physiol. **115**:548-555, 1936.
4. Elsom, K. A.; Bott, P. A., and Walker, A. M.: The simultaneous measurement of renal blood flow and the excretion of hippuran and phenol red by the kidney. Am. J. Physiol. **118**:739-742, 1937.
5. Cumming, R. E., and Chittenden, G. E.: Intravenous and retrograde urography; comparative study. J. A. M. A. **106**:602-606, 1936.
6. Quinby, W. C.: A note on the injection of sulfanilamide into the renal pelvis. Tr. Am. A. Genito-Urin. Surgeons (in press).

NEUROSYPHILIS AND ITS TREATMENT*

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BOSTON

IT IS a regrettable fact that discussion of syphilis of the nervous system and its treatment is still necessary. This, of course, would not be so if every patient with primary or secondary syphilis were promptly and adequately treated. It is the aim of the medical profession and the public-health service to eradicate syphilis. The means to accomplish this aim are at hand, but as yet there has been insufficient education of the public in regard to the necessity of proper treatment and public-health measures, and the medical profession is not sufficiently conversant with what constitutes adequate treatment. Syphilis at the present time is the direct cause of 5 or 10 per cent of all new admissions to psychopathic hospitals,[1] and of an equal percentage of admissions to general neurological wards.[2] Even if our most optimistic hopes are realized, several decades will have passed before there is any appreciable decrease in these percentages. Therefore discussion of neurosyphilis is still necessary.

Syphilis of the nervous system can be classified pathologically into meningeal, vascular and parenchymatous, according to the element of the nervous system most seriously involved. This classification is also of value in understanding the principles underlying treatment. It must be emphasized that these classifications are not mutually exclusive and that many cases show a mixture of two or all three types.

MENINGEAL NEUROSYPHILIS

It is safe to say that the meninges are primarily invaded in all cases of neurosyphilis. The fact is of extreme importance, because this involvement can be recognized in the early stages of the disease by examination of the cerebrospinal fluid, and proper treatment will prevent the spread of the infection to the blood vessels and parenchyma of the nervous system. Syphilis of the meninges may be subdivided into two groups, symptomatic and asymptomatic, according to whether signs or symptoms are present or the involvement is found only by examination of the cerebrospinal fluid.

Symptoms of involvement of the meninges may appear at any time after the infection,[3] but in the vast majority of cases they appear within the first two years. These signs and symptoms are headache, stiff neck, mental confusion and cranial nerve palsies. Fortunately, these signs and symptoms, with a few exceptions, are of relatively minor import to the life or economic independence of the patient, and respond quite readily to treatment. Removal of the cerebrospinal fluid by lumbar puncture and routine treatment by an arsenical and bismuth will relieve the symptoms and most of the signs of the meningeal involvement within a few weeks. Unfortunately, this dramatic improvement often deceives the patient, and sometimes the physician, into thinking that the disease is cured, whereas in fact the battle has only just begun. Treatment must be continued for at least eighteen months; and longer if the cerebrospinal fluid is not entirely normal by the end of that time.

Symptomatic involvement of the meninges (syphilitic meningitis) is a relative rarity, but either this or asymptomatic involvement (asymptomatic neurosyphilis) is always present before the development of parenchymatous neurosyphilis, and is only rarely absent in the cases that later develop signs of vascular neurosyphilis. It must be emphasized again that this fact is of extreme significance for the management of a patient with syphilis. The cerebrospinal fluid must be examined in every such patient. In primary or secondary syphilis this examination should be deferred until the patient has received treatment for a year to a year and a half, since a negative finding in the early stage does not necessarily indicate that there will not be later involvement, and also, positive findings in the early stages would not materially influence the method of treatment. On the other hand, the presence of a negative cerebrospinal fluid two or more years after the infection is almost absolute assurance that parenchymatous neurosyphilis will never develop, and a positive fluid at that stage is a serious warning of this danger, depending on the severity of the changes in the fluid,[4] and calls for continuation of therapy with or without modification until the fluid is entirely normal. In line with the above remarks, the cerebrospinal fluid should be examined immediately in all patients with latent syphilis two or more years after the infection, or with signs or symptoms of tertiary syphilis of the skin, bones or viscera. The duration and mode of treatment

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of such cases often depend on the results of this examination.

The method of treatment of patients with asymptomatic involvement of the meninges varies somewhat in different clinics. Some authorities prefer to use tryparsamide immediately, but it is my practice to treat such patients with ten to twenty injections of neoarsphenamine (0.3 to 0.75 gm.) at weekly intervals, followed by a similar number of injections of bismuth (1 or 2 cc.) at weekly intervals. This alternation of courses is repeated until the cerebrospinal fluid is entirely normal. The cerebrospinal fluid is controlled by examination at intervals of four to eight months. Tryparsamide is substituted for the neoarsphenamine at the end of one year of treatment if there has not been a marked diminution in the severity of the alterations in the cerebrospinal fluid. Fever therapy is considered if the fluid shows little progress toward normality after another year of tryparsamide and bismuth therapy.

VASCULAR NEUROSYPHILIS

Signs or symptoms of involvement of the blood vessels of the brain or spinal cord may develop at any time after the infection. They are occasionally present at the same time as the early meningeal symptoms, but are commoner several or many years later. The signs of cerebral vascular neurosyphilis are similar to those found in arteriosclerotic disease of the cerebral vessels. Syphilis should be suspected whenever a young or middle-aged individual develops signs or symptoms indicating thrombosis of a cerebral vessel. The disease is quite probable if there is no evidence of hypertension or cardiorenal disease. The diagnosis is established by the results of blood tests and examination of the cerebrospinal fluid. It must be remembered that changes in the fluid may be of any degree of severity or be entirely absent, depending chiefly on the amount of accompanying syphilitic meningitis.

Syphilitic involvement of the blood vessels of the spinal cord usually produces varying degrees of spinal myelitis, with pains, spasticity and weakness of the legs, or a complete transverse myelitis with a flaccid paraplegia. Multiple sclerosis and spinal-cord neoplasms are usually considered in the differential diagnosis, and the diagnosis can only be made by examination of the cerebrospinal fluid.

The treatment of vascular neurosyphilis is the same as that outlined for meningeal neurosyphilis. Dramatic results cannot be expected. The most that can be accomplished is the clearing up of any inflammatory reaction. The degree of functional recovery depends to some extent on how much of the symptomatology is produced by the inflammatory exudate, but mostly on the size and number of thrombosed vessels.

PARENCHYMATOUS NEUROSYPHILIS

Parenchymatous neurosyphilis usually takes the form of paretic or tabetic neurosyphilis. Other rarer forms are primary optic atrophy and chronic anterior poliomyelitis.

Paretic neurosyphilis (dementia paralytica, syphilitic meningoencephalitis) is the most serious form of syphilis of the nervous system. If untreated, it leads inevitably to dementia and death, and if not arrested in time, to partial dementia and economic dependence. The cardinal symptoms of this disease are changes in personality and evidences of mental deterioration. Convulsive seizures and transient focal neurologic signs are not uncommon. With progress, the disease may simulate any one of the known psychoses. Neurological examination of the patient often reveals only tremor of the mouth and tongue and hyperactive reflexes. The diagnosis is made on the appearance of signs and symptoms of organic mental disease and by results of examination of the cerebrospinal fluid, which always shows the characteristic abnormalities.

The results of treatment of paretic neurosyphilis with the arsphenamines and the heavy metals have been very disappointing, and it was not until the introduction of fever therapy by Wagner von Jauregg[5] and tryparsamide by Jacobs and Heidelberger[6] that any progress was made in the treatment of this disease. With these newer methods, it can be arrested in over 50 per cent of cases, and more than 30 per cent of patients[7] can be restored to their former station in society. The decision as to what mode of therapy — tryparsamide or fever — is to be used in a given case depends on the status of the patient at the time the diagnosis is made. If there are only mild personality changes or minor evidences of mental deterioration and the patient is able to continue his work, treatment with tryparsamide (1 to 3 gm. at weekly intervals) can be tried. If there is no further progress of the disease, the treatment can be confined to tryparsamide. Two to five years of treatment are necessary, and occasional examinations of the spinal fluid are of value in estimating the progress of the treatment. If satisfactory progress is not being made in the arrest of the disease as manifested by increase in symptoms, the patient should be hospitalized and fever therapy given. Fever therapy is immediately indicated if the patient presents himself with moderate or marked mental deterioration and is unable to work.

The common modes of fever therapy in use in

this country are the induction of malarial fever by inoculation with malaria organisms and the artificial induction of fever by heat cabinets.[8] There has been a great deal of argument as to the relative value of these two modes of therapy, but the results are quite comparable and the choice depends on the facilities at hand. The heat cabinets are quite expensive and require a great deal of technical and nursing assistance, while malaria can be given to a patient in any general hospital. The mortality rates for the two forms of treatment are not appreciably different. Fever therapy should always be followed by treatment with tryparsamide or one of the trivalent arsenicals for a period of two to five years, depending on the clinical progress of the patient and the rapidity of the reversal of the spinal fluid to normal.

Tabetic neurosyphilis (tabes dorsalis), like paretic neurosyphilis, is a late manifestation of the disease. The symptoms usually develop five to thirty years after the initial lesion. The early symptoms are lightning pains in the extremities, difficulty in walking, especially in the dark, and disturbance of the control of the urinary bladder. With progress of the disease there may be very marked ataxia and weakness of the lower extremities, atrophy of the optic nerves, other cranial nerve palsies, gastric and visceral crises, trophic ulcers and Charcot joints. Neurological examination of the patients shows a diminution or absence of the reflexes in the lower extremities, impaired vibratory and position sense in the legs, abnormal pupillary reactions[9] and changes in the cerebrospinal fluid.

The treatment of tabetic neurosyphilis is poorly standardized in comparison to that of paretic neurosyphilis. Fortunately, the course of the former is benign in comparison to that of the latter, leading to death only in rare cases, and not infrequently coming to a spontaneous arrest, leaving residual scars in the form of absent reflexes, impaired pupillary reactions and a varied degree of ataxia, impaired bladder function or cranial nerve palsies. Good results can be obtained in some early cases by routine treatment with the trivalent arsenicals and bismuth. Better results are usually obtained by the use of tryparsamide. Tryparsamide, of course, cannot be given when there are signs or symptoms of involvement of the optic nerve. Failure to respond to the intravenous treatment indicates that fever therapy should be tried. This should be followed by intravenous and intramuscular injections, as in the case of paretic neurosyphilis. The introduction of salvarsan serum intraspinally (Swift-Ellis treatment) which was in vogue several decades ago has waned in popularity, and has been replaced in practically all clinics by tryparsamide or fever therapy.

The results of treatment of tabes dorsalis are not so dramatic as those obtained in the treatment of paretic neurosyphilis. Usually the progress of the disease can be arrested, but the troublesome symptoms — gastric crises, lightning pains and so forth — may continue. Also the results of the treatment of the optic atrophy of tabes dorsalis and the primary optic atrophy of syphilis are disappointing. All forms of treatment have been tried in such patients, but good results are reported in only a small percentage. Tryparsamide is contraindicated, and if the progress of the atrophy is not interrupted by routine treatment with neoarsphenamine and bismuth, fever therapy should be used.

SUMMARY

Involvement of the nervous system can and should be prevented by the prompt and adequate treatment of primary and secondary syphilis. Serious damage to the nervous system can be prevented by the energetic treatment of patients with symptomatic or asymptomatic evidence of involvement of the meninges.

The therapeutic agents of value in neurosyphilis are those used in the treatment of syphilis elsewhere in the body with the addition of pentavalent arsenicals (tryparsamide) and fever therapy. The duration of treatment of neurosyphilis is not measured in weeks but in months and years.

REFERENCES

1. Moore, M., and Merritt, H. H.: Role of syphilis of the nervous system in the production of mental disease; survey of various forms of neurosyphilis occurring in Boston Psychopathic Hospital from 1912 to 1934. J. A. M. A. **107**:1292, 1936.
2. Merritt, H. H., and Moore, M.: The problem of syphilis on the wards of a large general hospital. New Eng. J. Med. **219**:834, 1938.
Editorial: Incidence and cost of syphilis. *Ibid.* **219**:857, 1938.
3. Merritt, H. H., and Moore, M.: Acute syphilitic meningitis. Medicine **14**:119-183, 1935.
4. O'Leary, P. A., et al.: Co-operative clinical studies in the treatment of syphilis; asymptomatic neurosyphilis. Arch. Dermat. & Syph. **35**:387-401, 1937.
5. Jauregg, J. W. von: Ueber die Einwirkung der Malaria auf die progressive Paralyse. Psych.-neurol. Wchnschr. **20**:132-134 and 251-256, 1918.
6. Jacobs, W. A., and Heidelberger, M.: Aromatic arsenic compounds. J. Am. Chem. Soc. **41**:1581-1644, 1919.
7. Solomon, H. C., and Epstein, S. H.: Dementia paralytica; results of treatment with malaria in association with other forms of therapy. Arch. Neurol. & Psychiat. **33**:1008-1021, 1935.
8. Neymann, C. A.: *Artificial Fever Produced by Physical Means: Its development and application.* 294 pp. Springfield, Illinois, and Baltimore: Charles C Thomas, 1938.
9. Merritt, H. H., and Moore, M.: The Argyll Robertson pupil; an anatomic-physiologic explanation of the phenomenon, with a survey of its occurrence in neurosyphilis. Arch. Neurol. & Psychiat. **30**:357-373, 1933.

REPORT ON MEDICAL PROGRESS

DISEASES OF THE THYROID GLAND

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IT HAS been requested that the authors of these reviews be selective and critical rather than comprehensive in the treatment of their subjects; also that they stress the practical rather than the theoretical, the former being presumably of more interest to practitioners. I shall attempt to abide by this request in so far as seems reasonable. I cannot, however, refrain from submitting that sound practice is usually the fruit of sound theory, and that if the practitioner is not interested in the scientific basis of his art, he ought to be. As a matter of fact, I believe that the practitioner is interested in scientific groundwork, and shall therefore have something to say about it in what follows. Indeed, did I not do this there would not be much material for review, because no evidence has been found that significant advances have been made during the last year in the diagnosis and treatment of diseases of the thyroid gland.

The surgery of the thyroid, for example, which has already reached a high degree of perfection, has not significantly altered, even in the last several years, except in so far as gradual improvement in the evaluation of operability of patients and in the niceties of preoperative and postoperative care, anesthesia and operative technic has reduced mortality and postoperative complications. What can be accomplished along these lines in the case of toxic goiter is excellently set forth in the papers of Sir Alan Newton,[1, 2] to which the reader is referred. So perfect, indeed, has thyroid surgery become that it seems that it has almost reached its limit, and that further progress in the therapeutics of thyroid diseases will be along lines other than surgical.

Endocrinological research, by contrast, has been almost hectically active, so much so, in fact, that it is almost impossible to keep up to date on its progress. Of course, many results are incomplete and experiments poorly conceived or controlled, yet out of the mass of material produced it is possible to draw certain new conceptions of the morbid physiology of the thyroid gland which are bound sometime, if not immediately, to alter our methods of diagnosis and treatment of its diseases. A huge literature is accumulating, for example, on the thyrotropic hormone produced by the anterior lobe of the pituitary. The appearance of this principle on the endocrinological scene has, among other things, revived active interest in the etiology of Graves's disease. Indeed, in considering these days, any disease of the thyroid gland which involves a disturbance in its function, orientation can perhaps be best achieved by thinking in terms of three substances and their physiologic actions and interactions, these being the thyroid hormone, the pituitary's thyrotropic hormone and the element iodine. That the pituitary's thyrotropic, or thyroid-stimulating, hormone regularly causes increased secretory activity of the thyroid gland, manifested morphologically by changes in the direction of hyperplasia and functionally by increased metabolic rate and other speed-ups characteristic of the action of thyroid hormone, is now well established. There is also evidence, though as yet less weighty, that the thyroid hormone exercises an inhibitory influence on the thyrotropic function of the anterior lobe of the pituitary (Aron,[3] Aron et al.,[4] Kuschinsky,[5] Marine[6, 7] and Gessler[8]). Should this evidence eventually prove correct, there emerges a functional equilibrium between two glands achieved by means of two hormones, one made by each gland and acting through its concentration in the blood on the other. The factors influencing such an equilibrium are obviously many: the rate of fixation, the destruction or excretion of the hormones, the development of antihormones and the action of neurogenic or humoral agents other than the hormones themselves on their rate of manufacture.

If we recall that Graves's disease is often precipitated by a psychic trauma, the question of whether either the thyroid or pituitary gland can be stimulated or inhibited in its secretory function directly through nervous pathways becomes of practical importance. Although it is well known that the thyroid gland has a rich innervation, the weight of evidence at the present time favors the view that this is not directly secretory, but rather vasomotor, and that secretory activity of the thyroid gland is not governed directly through nervous channels, but only humorally (Nonidez,[9, 10] Cahane and Cahane[11] and Uotila[12]). On the

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other hand, evidence is accumulating that the secretory activity of the pituitary gland can be influenced directly through nervous channels (Friedgood and Pincus[13]), and even that there are centers in the midbrain which control thyroid function via the anterior pituitary gland, the hook-up thus being first nervous, then humoral (Fenz[14] and Cahane and Cahane[11]).

These neurohormonal relations bear significantly on the etiology and pathogenesis not only of Graves's disease but also of myxedema. With the emergence of the pituitary's thyrotropic hormone, the question at once arises concerning both these diseases, Is the pituitary gland more to blame than the thyroid gland? In the case of Graves's disease certain writers, notably Marine,[6] early seized on the theory that this disease results from hyperfunction of the anterior lobe of the pituitary with respect to thyrotropic hormone. Others, such as Fellinger,[15] Spence,[16] Cope[17] and myself, hold to the view that at least ordinary Graves's disease is not caused primarily by hyperfunction of the anterior pituitary. It is possible, as Spence admits, that there are certain cases primarily pituitary in origin, and a larger group in which the thyroid hyperfunction is occasioned by some other mechanism. When a picture of Graves's disease is encountered as part of acromegaly, it seems reasonable to suppose that it is due primarily to anterior lobe hyperfunction. Important as is the question of which gland is chiefly at fault, it cannot at present be answered with finality because of the lack of satisfactory methods of study. The titers of the two hormones in the blood, if they could be determined accurately, might provide a solution of the problem, but as yet neither of them can be. Blood-iodine determinations can be made, to be sure, but there is great uncertainty (Salter[18]) concerning what fraction of total iodine represents hormone iodine, and indeed it is unknown in what form the hormone is carried in the blood stream. Lerman's[19] work suggests that it is not carried in the form of thyroglobulin, because with a serum immune to thyroglobulin he can detect no appreciable amount of that protein in the serum either of normal persons or of thyrotoxic or myxedematous subjects. Nor is he able to detect any thyroglobulin in human urine. It is highly interesting, although perhaps not as yet clarifying, that Salter and Lerman[20] were able to relieve myxedema completely with an iodinated indifferent protein such as serum albumin. Evidently the thyroidless individual is able to derive active hormone from such material. This fact increases the difficulty of interpreting blood-iodine values, and more than that, it may necessitate a complete reconstruction of our theory of the role of the thyroid gland in the manufacture of what has been called the thyroid hormone. Perchance instead of being the factory of the hormone, the gland is no more than its distributing warehouse.

When it comes to thyrotropic hormone the difficulties are still greater, because no chemical approach is available. Determination of thyrotropic activity of the material under investigation, by observation of its effect on the thyroid of a test animal, is all that is possible. This is called bioassay. It has the limitation that it discloses only the net amount of thyrotropic activity present—that is to say, the amount of thyrotropic activity over and above whatever antithyrotropic activity may be present. Nevertheless, a rapidly increasing number of bioassays for thyrotropic hormone in clinical cases are appearing in the literature (Aron et al.,[4] Krogh and Okkels,[21] Hertz and Oastler,[22] Fellinger,[15] Spence,[16] Emerson and Cutting,[23] Cope,[24] Starr et al.[25] and Jones[26]), and while there is much conflicting data, the results tend to show that there is less thyrotropic activity in the blood and urine of thyrotropic persons than in normal subjects, and rather more in that of persons who have been cured of thyrotoxicosis by subtotal thyroidectomy. Hertz and Oastler, using pituitarectomized rats as test objects, have found increased thyrotropic activity in the serum and urine of myxedematous patients. This has been partially confirmed by Starr et al., using intact guinea pigs as test objects.

In the recent literature there are also to be found numerous other types of investigations on thyrotropic hormone and antithyrotropic agents, and other factors which may influence the thyroid gland humorally. Thus, it has been shown that thyrotropic hormone selectively increases the metabolism of isolated thyroid tissue (Paal,[27] Anderson and Alt[28] and Canzanelli and Rapport[29]), and Williams[30] has shown that the secretory cycle of thyroid follicles, which he observed directly in autografts in the rabbit's ear, are accelerated by giving the animal material possessing thyrotropic activity. What seems a singularly important piece of work is that of Foot, Baker and Carrel,[31] in which human thyroid glands removed at operation were cultivated in toto in the Lindbergh apparatus. The significant result thus obtained was that the histological picture reached by the gland under such circumstances seemed determined, not by the phase of activity which had pertained while it resided in the body to which it belonged, but by the nature of the perfusate used during its existence in vitro. A possible implication of such findings is that in Graves's disease the

state of hyperplasia of the thyroid gland is the consequence of predominantly thyrotropic properties of the blood that reaches the gland, rather than that of any condition inherent in the gland itself. From the practical side, however, it can be said that in the patient the only agent which we as yet have by which, in Graves's disease, the thyroid gland can be beneficially affected humorally is iodine, and that our chief attack must still be aimed directly at the thyroid gland in the form of surgical resection or irradiation.

The mode of action of iodine in toxic goiter is still a matter of debate. My colleagues and I (Means and Lerman[32] and Means[33]) believe that its action is directly on the thyroid cells, whose function it alters by a blockade of some sort, leading to increased storage of hormone in the gland and decreased delivery to the body. Eason,[34] however, submits that there is no evidence that iodine acts directly on the thyroid cells, and there are some who believe that it acts primarily on the pituitary gland or even on the midbrain. One thing is clear, however: it does not act on circulating thyroid hormone. Giving iodine has no effect on thyrotoxicosis produced by the administration of thyroid extract.

Because of the essential role of iodine in thyroid economy, iodine tolerance tests of various sorts are rapidly making their appearance, designed both for investigative and for diagnostic purposes (Elmer,[35] Perkin, Brown and Lang,[36] Watson[37, 38] and Litchfield[39]). While these tests are yielding information of interest, the difficulties of interpretation of the significance of variously bound fractions of iodine in the blood stream, and the variance of results obtained by different methods, make me believe that not yet has this type of observation become of great diagnostic importance.

While we are on the subject of iodine, mention should be made of a new type of investigation of thyroid problems which depend on the use of iodine rendered radio-active, the course of which through the animal body, can be traced by virtue of its radio-activity. Hertz, Roberts, Means and Evans,[40, 41] in Boston, and Hamilton and Soley,[42] in San Francisco, have reported observations of this type. In animals it has been shown by the former that the thyroid gland traps iodine very rapidly and quickly becomes saturated with it. In certain types of hyperplasia of the thyroid gland, although the collection of iodine by the gland is greater than in normal conditions, the threshold for iodine uptake seems elevated. That is to say, certain hyperplastic glands are less able to utilize small quantities of iodine than are normal glands, but have the capacity of taking up more iodine from large doses. This may throw further light on the mechanism of Graves's disease, in that it explains how a gland known to have a great affinity for iodine still does not cure itself by taking up the small quantities of iodine normally found in the diet, but can be definitely benefited by the administration of relatively large amounts of iodine. Hertz and Roberts have also administered radio-active iodine to human subjects with goiter, and when the thyroid gland has been removed at operation, determined the amount collected by the gland and its chemical combination.

The hormonic pattern in myxedema is perhaps somewhat easier to visualize than is that of Graves's disease. Here again the possibility of a pituitary variety (hypofunction of the anterior lobe with respect to thyrotropic hormone) and a primary thyroid variety presents itself. The weight of evidence, as in Graves's disease, points strongly away from the pituitary gland in the usual case of myxedema. A primary thyroid atrophy seems to be the cause of classic myxedema, and the hormonic set-up a simple shortage of one hormone, that of the thyroid gland. It is becoming apparent, however, that there are exceptional cases (one has been reported by Castleman and Hertz,[43] and several others have been seen in my clinic) in which thyroid hypoplasia with a resulting picture of myxedema is secondary to lack of anterior lobe function. These cases may be indistinguishable at first sight from ordinary myxedema, although the presence of amenorrhea in place of the usual menorrhagia of myxedema is highly suggestive of a pituitary origin. The practical importance of the group is that on thyroid therapy they may do badly, may in fact go into a state of shock similar to that seen in Addison's disease, and due, indeed, to the aggravation of a subclinical hypocortinism of pituitary origin by the administered thyroid, quite analogous to the aggravation of diabetes seen in persons with both myxedema and diabetes when thyroid is administered. The point of practical importance is that it behooves the physician to study the hormonic signs in his patients which seem to be myxedematous, and in inaugurating thyroid therapy to proceed with caution and have the patient under close surveillance. When the type of reaction mentioned above is observed, it may be necessary to protect the patient with a high-salt diet and possibly cortin while administering thyroid, and the gonadotropic hormone of the anterior pituitary gland may be desirable as well.

In the older literature one finds accounts of the co-existence of myxedema and Graves's disease. Of course, it is impossible to have both too much

and too little thyroid hormone produced at the same time; nevertheless, it is possible for certain manifestations of Graves' disease, for example the eye signs, to be present at a time when the patient is unmistakably on the hypothyroid side, as for instance occasionally after extensive subtotal thyroidectomy. This fact leads naturally to a related one, namely, that in certain cases of Graves's disease the eye signs seem to become quite divorced from the thyrotoxic signs, and to vary independently as though of different causation. In a patient with no discoverable clinical signs of thyrotoxicosis one may see eye signs of marked degree, or in a patient originally thyrotoxic with slight eye signs one may observe progressive and serious exophthalmos after thyrotoxicosis has been completely abolished by thyroidectomy (Thomas and Woods[44] and Ginsburg[45]). One may even see marked eye signs in persons frankly myxedematous. Brain[46] has described the former picture under the title of "exophthalmic ophthalmoplegia," a not altogether satisfactory term because cases are not infrequently found, evidently of the same general nature as those described by him, in which there is no ophthalmoplegia. The clinical importance of this special subgroup of cases of Graves's disease is that in them the safeguarding of the eyes may be the major problem. In the more malignant types the orbital decompression operation of Naffziger[47, 48] may become necessary, but in many others the condition is fortunately less serious. Some evidence is accumulating that the administration of thyroid benefits the eye condition in some of these cases. Especially if the basal metabolic rate is low, thyroid can be tried quite freely. A possible theoretical explanation of a beneficial action of thyroid on the eyes under such circumstances would be that the eye signs are due to pituitary hyperfunction, as Marine[7] contends, and that thyroid inhibits the pituitary gland. When the basal metabolic rate is not below normal, good results have sometimes followed the combined use of thyroid and iodine. The iodine by direct action on the thyroid gland holds the basal metabolic rate at a lower level than would obtain in its absence, and this gives more opportunity to exhibit thyroid hormone without producing alimentary thyrotoxicosis. Whether this reasoning is sound is far from certain, but it is true that a number of patients have shown improvement under such combined treatment. Good results have also been claimed for irradiation of the orbit or the pituitary gland (Ginsburg[45]).

The relation of thyroid function to gonadal function has of late attracted much attention from both biological and clinical investigators. The thyroid hormone unquestionably affects all other endocrine glands, at least to the extent of accelerating the rate of metabolism of their cells, as it does that of all cells. This might be called a non-specific effect. Whether the thyroid hormone acts on other glands more specifically — we have already indicated that it may inhibit certain functions of the anterior lobe of the pituitary gland — is a question of both theoretical and practical importance. To the various speed-ups characteristic of thyroid hormone action can now be added the increased rate of egg-laying by hens receiving thyroid hormone (Winchester[49]) and of milk production by cows (Graham[50]). Whether these effects, which incidentally may be of the non-specific variety, constitute good news for dairy and poultry farmers, or whether the ill effects of thyroid feeding offset the increased yield, I am not competent to say. Perhaps those physicians who engage in gentleman farming for their release may answer the questions. That thyroid feeding renders certain sterile women fertile and enables certain habitual aborters to go through normal pregnancy has long been known (King and Herring[51]). Also long known in the field of thyro-ovarian relations are the menstrual patterns in myxedema (characteristically menorrhagia) and in thyrotoxicosis (characteristically oligorrhea or amenorrhea). Good results are reported in the treatment of various menstrual irregularities by thyroid (Foster and Thornton[52]). All these may also belong in the realm of non-specific action. More recently, however, there has been accumulating evidence of more specific effects. For example, Tyndale and Levin[53] found that the stimulation of ovarian follicles which ordinarily occurs when menopausal urine is injected into immature hypophysectomized rats was markedly decreased by the simultaneous injection of thyroxine. They concluded that the thyroid hormone exerts an inhibiting action on gonad stimulation which is a direct one and not mediated through the pituitary gland, since it was demonstrated in pituitarectomized animals. Membrives,[54] on the other hand, reports that the ability of implants of the anterior pituitary gland to cause ovarian development and consequent vaginal canalization in immature rats was increased by thyroid feeding and decreased by thyroidectomy. This may be a non-specific effect in contrast to that observed by Tyndale and Levin, which would appear to be specific. It is of interest, furthermore, that Gessler[8, 55] has shown that the ovarian hormone, folliculin (estrin), has the power to lower the basal metabolic rate of normal guinea pigs and that of hypophysectomized rats, a power which he attributes to an antithyroid property. Of course, such observations as these are fragmentary and

their medical significance is obscure, yet they are not without practical interest, for they may indicate a new approach, the hormonic, to the treatment of thyrotoxicosis. Indeed, Starr and Patton[56, 57] have already shown that remissions can be produced in hyperthyroidism by treatment with an extract of pregnancy urine. They do not undertake to explain the mechanism, but it seems fair to consider it related to the experimental results cited above, and perhaps due to a thyroinhibitory action of estrin which the gonadotropic activity of pregnancy urine would cause to be secreted in increased quantity.

A quite different indication of balance, or dependence, of function between the thyroid gland and gonads is to be found in the age and sex incidence of thyroid diseases. A recent paper by Bram[58] gives some interesting data. In children he finds the incidence of exophthalmic goiter is 1 boy to 20 girls, in young adults 1 man to 5 women and in elderly persons 1 man to 2 women.

Geographic incidence may also throw light on etiology. In the case of exophthalmic goiter such information has long been wanting. Now, however, Read[59] has supplied it. His studies disclose that the distribution of exophthalmic goiter, that is to say the morbidity of this disease, is far more uniform throughout the United States than is that of endemic goiter. This finding is strong evidence that the two diseases are etiologically unrelated. With regard to the etiology of endemic goiter, Kimball[60] claims that twenty years' experience with goiter prophylaxis proves that this disease is one purely of iodine deficiency, and preventable. The best method of prophylaxis is by iodized salt, and in preventing endemic goiter, according to Kimball, adenomas, toxic goiters, cretinism and deaf mutism are likewise prevented. In so far as Kimball's contention applies to exophthalmic goiter, I must dissent. The work of Read, cited above, seems to me to refute this portion of Kimball's argument. Nonetheless, goiter prophylaxis is one of the triumphs of modern medicine, and not only originated in the United States but has been conducted most successfully here. For example, Kimball points out that in Switzerland, where the iodized salt is poorer in iodine than that used in this country, the results have been less impressive.

The recent literature indicates considerable interest in the results of treatment of cretinism. Some writers are more optimistic than others. Most stress the importance of early diagnosis and thorough treatment. Lewis, Samuel and Galloway[61] claim that cretins can become mentally normal on treatment. They, however, point out that promptness and continuity of treatment are not the sole factors determining the degree of mental recovery. Other factors are degree of development at the time that symptoms appeared, cerebral damage at birth and hereditary endowment. That is to say, thyroid administration will not make the cretin any better mentally than he would have been had he not been a cretin. Brown, Bronstein and Kraines,[62] while admitting that early recognition and persistence in treatment are very important, find that even when these are achieved the majority of patients fail to attain normal mental growth. The chances, so these authors claim, that at maturity the mental age will be more than ten or eleven are not great. The curves of mental growth in treated cretins are of the same general shape as those in normal children, but lie at a lower level.

In this connection it is pertinent to note that thyroid hormone is in a sense a growth hormone. Not alone in cretins, but in certain pituitary dwarfs also, it promotes growth in a very satisfactory manner. On the experimental side Evans, Simpson and Pencharz[63] have shown that growth promotion secured by anterior pituitary extracts, although not dependent on the presence of the thyroid gland, is greater when it is present. Thyroxine, which promotes the growth of thyroidectomized animals, does not have this effect when administered to thyroidectomized pituitarectomized animals. A synergism exists between the anterior pituitary growth hormone and the thyroid hormone, which is independent of the anterior pituitary thyrotropic hormone.

In the non-endocrine, or perhaps better non-hormonic, varieties of thyroid disease, as for example cancer, inflammations and anomalies, I have found no contributions within the year sufficiently significant to rate mention in a review so restricted in length as is this one.

REFERENCES

1. Newton, A.: Toxic goitre, with special reference to end-results. M. J. Australia **2**:265-275, 1938.
2. *Idem:* The hospital management of patients suffering from thyrotoxicosis. Roy. Melbourne Hosp. Clin. Rep., December, 1938.
3. Aron, M.: Particularités histologiques de la réaction de la thyroïde aux extraits de lobe antérieur d'hypophyse. Compt. rend. Soc. de biol. **103**:145-147, 1930.
4. Aron, M.; Van Caulaert, C., and Stahl, J.: L'équilibre entre l'hormone préhypophysaire et l'hormone thyroïdienne dans le milieu intérieur, à l'état normal et à l'état pathologique. Compt. rend. Soc. de biol. **107**:64-66, 1931.
5. Kuschinsky, G.: Ueber die Bedingungen der Sekretion des thyreotropen Hormons der Hypophyse. Arch. f. exper. Path. u. Pharmakol. **170**:510-533, 1933.
6. Marine, D.: Physiology and principal interrelations of thyroid. J. A. M. A. **104**:2250-2255, 1935.
7. *Idem:* Does the study of experimental exophthalmos offer any clue to the fundamental nature of Graves' disease? Tr. Third Internat. Goiter Conf. & Am. A. for Study of Goiter, pp. 7-16, 1938.
8. Gessler, C.: Activité antithyroïdienne de la folliculine; role de l'hypophyse. Arch. internat. de pharmacodyn. et de thérap. **55**:267-281, 1937.
9. Nonidez, J. F.: Innervation of the thyroid gland. III. Distribution and termination of the nerve fibers in the dog. Am. J. Anat. **57**:135-169, 1935.
10. *Idem:* Nervous "terminal reticulum." Critique: observations on thyroid and liver. Anat. Anz. **84**:1-13, 1937.
11. Cahane, M., and Cahane, T.: Sur l'existence des centres nerveux infundibulaires réglant la fonction du corps thyroïde. Acta med. Scandinav. **94**:320-327, 1938.

12. Uotila, U. U.: Rôle of cervical sympathetics in the regulation of thyroid and thyrotropic function. Endocrinology **25**:63-70, 1939.
13. Friedgood, H. B., and Pincus, G.: Studies on conditions of activity in endocrine organs. XXX. The nervous control of the anterior hypophysis as indicated by maturation of ova and ovulation after stimulation of cervical sympathetics. Endocrinology **19**:710-718, 1935.
14. Fenz, E.: Ueber die Wirkung der Zwischenhirnnarkose bei Morbus Basedow. Wien. Arch. f. inn. Med. **30**:15-56, 1937.
15. Fellinger, K.: Klinische und experimentelle Untersuchungen über das Verhalten und die Bedeutung des thyreotropen Hormons im Blute. Wien. Arch. f. inn. Med. **29**:375-406, 1936.
16. Spence, A. W.: discussion of Loeser, A.: Hyperthyroidism and the thyrotropic hormone of the pituitary. Brit. M. J. **1**:1276-1278, 1937.
17. Cope, C. L.: discussion of Loeser, A.: Hyperthyroidism and the thyrotropic hormone of the pituitary. Brit. M. J. **1**:1276-1278, 1937.
18. Salter, W. T.: Fluctuations in body iodine. Physiol. Rev. (in press).
19. Lerman, J.: personal communication.
20. Salter, W. T., and Lerman, J.: Iodinated protein in human athyreosis. Tr. A. Am. Physicians **53**:202-209, 1938.
21. Krogh, M., and Okkels, H.: L'hormone thyréostimulante préhypophysaire est-elle présente dans l'urine? Compt. rend. Soc. de biol. **113**:635-638, 1933.
22. Hertz, S., and Oastler, E. G.: Assay of blood and urine for thyrotropic hormone in thyrotoxicosis and myxedema. Endocrinology **20**:520-525, 1936.
23. Emerson, K., Jr., and Cutting, W. C.: Urinary thyrotropic hormone. Endocrinology **23**:439-445, 1938.
24. Cope, C. L.: The anterior pituitary lobe in Graves' disease and in myxoedema. Quart. J. Med. **7**:151-170, 1938.
25. Starr, P.; Rawson, R. W.; Smalley, R. E.; Doty, E., and Patton, H.: The microhistometric method applied to thyrotropic hormone assay. West. J. Surg. **47**:65-75, 1939.
26. Jones, M. S.: A study of thyrotropic hormone in clinical states. Endocrinology **24**:665-671, 1939.
27. Paal, H.: Ueber die hormonale Beeinflussung des Stoffwechsels von überlebendem Schilddrüsengewebe. Arch. f. exper. Path. u. Pharmakol. **173**:513-525, 1933.
28. Anderson, R. K., and Alt, H. L.: The effect of thyrotropic pituitary hormone on the oxygen consumption of thyroid tissue in vitro. Am. J. Physiol. **119**:67-69, 1937.
29. Canzanelli, A., and Rapport, D.: The effect of thyrotropic hormone, alone and with other substances, on the in vitro oxygen consumption of thyroid and liver. Endocrinology **22**:73-79, 1938.
30. Williams, R. G.: Microscopic studies of living thyroid follicles implanted in transparent chambers installed in rabbit's ear. Am. J. Anat. **62**:1-29, 1937.
31. Foot, N. C.; Baker, L. E., and Carrel, A.: The behavior of abnormal human thyroid tissue cultivated in the Lindbergh apparatus. J. Exper. Med. **70**:39-51, 1939.
32. Means, J. H., and Lerman, J.: The curves of thyroxine decay in myxedema and of iodine response in thyrotoxicosis: their similarity and its possible significance. Ann. Int. Med. **12**:811-820, 1938.
33. Means, J. H.: On the pathogenesis of Graves' disease. Proc. Staff Meet., Mayo Clin. **12**:11-16, 1937.
34. Eason, J.: Primary toxic goitre. Edinburgh M. J. **45**:529-539, 1938.
35. Elmer, A. W.: Iodine tolerance test for thyroid insufficiency. Endocrinology **18**:487-496, 1934.
36. Perkin, H. J.; Brown, B. R., and Lang, J.: The blood iodine content of normal and thyrotoxic individuals: an iodine tolerance test. Canad. M. A. J. **31**:365-368, 1934.
37. Watson, E. M.: An iodine tolerance test for the investigation of thyroid function. Endocrinology **20**:358-362, 1936.
38. *Idem:* The relation of the iodine tolerance to thyroid function. Endocrinology **22**:528-537, 1938.
39. Litchfield, H. R.: The value of blood iodine determination from a clinical viewpoint. Tr. Third Internat. Goiter Conf. & Am. A. for Study of Goiter, pp. 414-423, 1938.
40. Hertz, S.; Roberts, A., and Evans, R. D.: Radioactive iodine as an indicator in the study of thyroid physiology. Proc. Soc. Exper. Biol. & Med. **38**:510-513, 1938.
41. Hertz, S.; Roberts, A.; Means, J. H., and Evans, R. D.: Radioactive iodine as an indicator in thyroid physiology. II. Iodine collection by normal and hyperplastic thyroids in rabbits. Am. J. Physiol. (in press).
42. Hamilton, J. G., and Soley, M. H.: Studies in iodine metabolism by the use of a new radio-active isotope of iodine. Am. J. Physiol. **126**:521P, 1939.
43. Castleman, B., and Hertz, S.: Pituitary fibrosis with myxedema. Arch. Path. **27**:69-79, 1939.
44. Thomas, H. M., Jr., and Woods, A. C.: Progressive exophthalmos following thyroidectomy. Bull. Johns Hopkins Hosp. **59**:99-113, 1936.
45. Ginsburg, S.: Postoperative progressive exophthalmos with low basal metabolic rate. Ann. Int. Med. **13**:424-450, 1939.
46. Brain, W. R.: Exophthalmic ophthalmoplegia. Quart. J. Med. **7**:293-323, 1938.
47. Naffziger, H. C.: Progressive exophthalmos following thyroidectomy: its pathology and treatment. Tr. Am. S. A. **49**:168-172, 1931.
48. *Idem:* Pathologic changes in the orbit in progressive exophthalmos; with special reference to alterations in the extra-ocular muscles and the optic disks. Arch. Ophth. **9**:1-12, 1933.
49. Winchester, C. F.: Influence of thyroid on egg production. Endocrinology **24**:697-701, 1939.
50. Graham, W. R., Jr.: The effect of thyroidectomy and thyroid feeding on the milk secretion and milk fat production of cows. J. Nutrition **7**:407-429, 1934.
51. King, E. L., and Herring, J. S.: Hypothyroidism in the causation of abortion, especially of the "missed" variety. J. A. M. A. **113**:1300-1302, 1939.
52. Foster, R. C., and Thornton, M. J.: Thyroid in the treatment of menstrual irregularities. Endocrinology **24**:383-388, 1939.
53. Tyndale, H. H., and Levin, L.: Ovarian weight responses to menopause urine injections in normal, hypophysectomized and hypophysectomized thyroxin-treated immature rats. Am. J. Physiol. **120**:486-493, 1937.
54. Membrives, J. R.: Thyroïde et pouvoir gonadotropique de l'hypophyse du rat. Compt. rend. Soc. de biol. **127**:695-697, 1938.
55. Gessler, C.: Influence of folliculin on the basal metabolic rate. Arch. internat. de pharmacodyn. et de thérap. **54**:263-271, 1936.
56. Starr, P., and Patton, H.: The effect of pregnancy urine extract and ovarian follicular hormone on hyperthyroidism. Endocrinology **18**:113-116, 1934.
57. *Idem:* Observations of remissions in hyperthyroidism induced by pregnancy urine extract. Ann. Int. Med. **8**:825-833, 1935.
58. Bram, I.: Exophthalmic goiter in patients past age fifty: comments based on a series of 322 cases. Pennsylvania M. J. **42**:117-120, 1938.
59. Read, J. M.: Studies in exophthalmic goiter. I. Its incidence throughout the United States. Arch. Int. Med. **63**:71-79, 1939.
60. Kimball, O. P.: Twenty years in the prevention of goiter (1916-1936). Tr. Third Internat. Goiter Conf. & Am. A. for Study of Goiter, pp. 57-63, 1938.
61. Lewis, A.; Samuel, N., and Galloway, J.: A study of cretinism in London: with especial reference to mental development and problems of growth. Lancet **1**:1505-1509, and **2**:5-9, 1937.
62. Brown, A. W.; Bronstein, I. P., and Kraines, R.: Hypothyroidism and cretinism in childhood. VI. Influence of thyroid therapy on mental growth. Am. J. Dis. Child. **57**:517-523, 1939.
63. Evans, H. E.; Simpson, M. E., and Pencharz, R. I.: Relation between the growth promoting effects of the pituitary and the thyroid hormone. Endocrinology **24**:875, 1939.

VERMONT STATE MEDICAL SOCIETY

HOUSE OF DELEGATES

THE opening session of the House of Delegates of the Vermont State Medical Society was called to order by the president, Dr. F. J. Lawless, at 8:00 p. m., Wednesday, October 4, 1939, in the Roof Garden of the Hotel Vermont, Burlington.

President Lawliss appointed as the Credentials Committee:

Dr. H. L. Frost, Pittsford
Dr. F. J. Hurley, Bennington
Dr. F. L. Hall, Grand Isle

He requested the members to present their credentials to this committee. The roll was called by the Secretary. Dr. G. O. Pratt moved that the by-laws be suspended and Dr. C. C. Shaw, Dr. W. H. McBride and Dr. Henry Baby be seated as members. Delegates present were as follows:

Addison County	V. W. Waterman, Vergennes S. S. Eddy, Middlebury
Bennington County	F. J. Hurley, Bennington
Chittenden and Burlington Counties	E. H. Buttles, Burlington E. D. McSweeney, Burlington A. B. Soule, Jr., Burlington E. G. Twitchell, Burlington Lyman Allen, Burlington C. K. Johnson, Burlington R. L. Maynard, Burlington F. L. Hall, Grand Isle
Franklin County	T. Edwin Kirk, St. Albans Henry Baby, St. Albans G. O. Pratt, Richford
Lamoille County	L. P. Holcomb, Johnson
Northeastern County	W. H. McBride, Island Pond D. E. Coburn, St. Johnsbury F. E. Farmer, St. Johnsbury W. B. Fitch, St. Johnsbury C. G. Schurman, Newport
Rutland County	R. H. Seeley, Rutland H. L. Frost, Pittsford Edward Rogers, Pittsford W. C. Hammond, Rutland E. J. Quinn, Castleton
Washington County	A. B. Warren, Hardwick
Windham County	R. E. McSweeney, Brattleboro C. C. Shaw, Bellows Falls
Windsor County	Wayne Griffith, Chester Paul Bacon, Springfield

The report of the Secretary was read, and accepted as read. The reports of the various committees were accepted as written in the *Annual Report.*

Dr. B. F. Cook reported that the president of the Society, Dr. E. A. Hyatt, was ill, and Dr. R. E. McSweeney was appointed to draft a telegram to Dr. Hyatt, which read as follows: "The House of Delegates of the Vermont State Medical Society wish to express their sincere regret at your inability to be present with us as our president, and wish you a speedy recovery."

A motion was made by Dr. Wayne Griffith that the President appoint a committee of five members to study thoroughly the present Medical Practice Act in the State of Vermont, and that this committee report to the House of Delegates in 1940 with recommendations for action, and that any expenses incurred by the committee be paid by the Society. This was seconded by Dr. A. B. Soule, Jr., and so passed.

Dr. Paul Bacon moved that the constitution and by-laws brought up for repeal last year be repealed. The motion was seconded by Dr. R. H. Seeley, and so passed. Dr. E. D. McSweeney, in accordance with a motion made in 1938 that the constitution and by-laws be redrafted by a committee consisting of Dr. Hyatt, Dr. E. H. Buttles and Dr. McSweeney, read some of the outstanding changes in the revised constitution.

Dr. McSweeney made a motion, which Dr. Seeley seconded, that a committee of three be appointed to report back later in the evening on the revised constitution and by-laws. Dr. Buttles, Dr. Seeley and Dr. Soule were appointed.

Dr. E. D. McSweeney reported that he had examined the model constitution which Dr. Cook had submitted, made minor revisions and returned it to Dr. Cook. It was printed and sent to each county society with the recommendation that each society hold its annual meeting in July or early August so that all delegates might be properly certified under the legislations of the present by-laws. Dr. R. E. McSweeney reported that Windham County had accepted the new constitution with some revisions, one being that the annual meeting would be held early in January. A discussion on the old and new constitutions followed.

A discussion on the filing of birth certificates with regard to crippled children was held with Dr. C. G. Schurman, Dr. Soule and Dr. C. K. Johnson taking part.

The Resolutions Committee was appointed by the President to consist of:

Paul Bacon, Springfield
Henry Baby, St. Albans
C. K. Johnson, Burlington

Dr. Edward Rogers objected to voting on the constitution without first reading it. A discussion followed. Dr. Soule approved the constitution with a few minor changes. Dr. E. J. Quinn made a motion that copies be mimeographed and given to each delegate. This was seconded by Dr. Harry Frost, voted on, and so passed.

The question of members of the Society who had passed a certain age being carried as honorary members, exempt from dues, was discussed by Dr. R. L. Maynard, Dr. Buttles and Dr. E. D. McSweeney. No action was taken.

Dr. Cook invited the members to Rutland for the 1940 meeting. Dr. Schurman made a motion that the meeting be held in Burlington. Dr. R. E. McSweeney invited the Society to Brattleboro, and Dr. F. J. Hurley extended an invitation to Bennington. Dr. C. C. Shaw moved that the invitation of Dr. Cook be accepted. This was seconded by Dr. Johnson, voted on, and carried.

Dr. Lyman Allen made a motion to rescind the motion that the old constitution be repealed and Dr. Johnson seconded the motion, which was carried.

Dr. R. L. Maynard moved that the afternoon of the second day of the annual meeting be devoted to definite groups of members, who might wish to put on speakers of their own, the expense to be paid by the Society. Dr. R. E. McSweeney seconded the motion, and after a discussion the motion was defeated.

Dr. Soule made a motion that an additional half day be given over to various groups that would like to have their own speakers and that each group should finance its own portion. The motion was voted on and carried.

Dr. Soule, Dr. F. E. Farmer and Dr. W. H. McBride were appointed as a nominating committee and were requested to report the next day.

Dr. Cook brought up the subject of a medical library again, and Dr. Bacon made a motion that one hundred and fifty dollars be placed at the discretion of the Secretary to secure literature pertaining to early Vermont medical history. Dr. Farmer seconded the motion, and it was carried.

A discussion on dues concluded the discussions.

A motion to adjourn was made, seconded and carried.

* * *

The adjourned session of the House of Delegates of the Vermont State Medical Society was called to order by the president, Dr. F. J. Lawliss, at 1:00 p. m., Thursday, October 5, in the Hotel Vermont.

Twenty-three members responded to the roll call.

The report of the secretary, Dr. Cook, was accepted as read. Dr. Cook received an answer to the telegram, which was sent to Dr. Hyatt, which read as follows: "Please express to the House of Delegates my appreciation of their good wishes. Tell the convention I shall greatly miss renewing my many pleasant acquaintances, and that I greatly regret my inability to perform my duties as your president."

The report of the Nominating Committee was as follows:

PRESIDENT — C. F. Ball, Rutland

PRESIDENT-ELECT — A. M. Cram, Bridgewater

VICE-PRESIDENT — W. W. Angell, Randolph

SECRETARY — B. F. Cook, Rutland

TREASURER — David Marvin, Essex Junction

AUDITOR — T. S. Brown, Burlington

COUNCILORS

1st District — L. E. Sample, St. Albans
2d District — R. E. Seeley, Rutland
3d District — F. E. Farmer, St. Johnsbury
4th District — A. M. Cram, Bridgewater

CANCER COMMITTEE

C. F. Ball (chairman), Rutland (3 years)
J. H. Woodruff, Barre (2 years)
W. W. Angell, Randolph (1 year)

EXECUTIVE COMMITTEE

B. F. Cook (chairman), Rutland
G. B. Smith, Rutland
R. E. Seeley, Rutland

HEALTH AND PUBLIC INSTRUCTION COMMITTEE

P. D. Clark (chairman), Burlington
C. G. Abell, Enosburg Falls
L. J. Wainer, Hinesburg

LEGISLATIVE COMMITTEE

R. E. McSweeney (chairman), Brattleboro
F. J. Hurley, Bennington
A. B. Soule, Jr., Burlington

LIBRARY COMMITTEE

W. H. McBride, Island Pond
Lyman Allen, Burlington
G. G. Marshall, Rutland

MATERNAL AND CHILD HEALTH COMMITTEE

H. A. Durfee (chairman), Burlington
Emily T. Wilson, St. Johnsbury
R. E. Corley, Burlington

NECROLOGY COMMITTEE

C. F. Dalton (chairman), Burlington
G. G. Marshall, Rutland

PUBLICATIONS COMMITTEE

B. F. Cook (chairman), Rutland
H. E. Upton, Burlington
C. F. Ball, Rutland

PUBLIC RELATIONS COMMITTEE

F. E. Farmer, St. Johnsbury (3 years)
Stewart Ross, Rutland (2 years)
E. A. Hyatt, St. Albans (1 year)

DELEGATES TO THE AMERICAN MEDICAL ASSOCIATION

Delegate — B. F. Cook, Rutland
Alternate — C. G. Abell, Enosburg Falls

DELEGATES TO OTHER STATES

Massachusetts — R. E. McSweeney, Brattleboro
New York — C. H. Beecher, Burlington
New Hampshire — A. M. Cram, Bridgewater
Maine — C. G. Schurman, Newport
Connecticut — F. E. Farmer, St. Johnsbury
Rhode Island — Philip Wheeler, Brattleboro

HOUSE OF DELEGATES — OFFICERS

President — E. D. McSweeney, Burlington
First vice-president — C. G. Schurman, Newport
Second vice-president — Paul Bacon, Springfield

ANNIVERSARY CHAIRMAN

Stewart Ross, Rutland

A motion was made by Dr. Buttles that the report of the Nominating Committee stay on the table until the question of the constitution was decided. This was seconded and so passed.

President Lawliss appointed the following as members of the committee to report on the Medical Practice Act:

F. J. Hurley (chairman), Bennington
A. B. Soule, Jr., Burlington
H. E. Upton, Burlington
R. E. McSweeney, Brattleboro
Wayne Griffith, Chester

Dr. Farmer moved that the old constitution be revoked but that it should stay in effect until the new constitution was adopted. The motion was seconded and carried.

Dr. Soule moved to have the new constitution adopted as presented by the committee which drafted it, with the exception of an amendment to Section 1, Paragraph 2, as follows: "That at the annual meeting a president, president-elect, vice-president, secretary, treasurer and auditor shall be elected." Dr. H. L. Frost seconded this motion, and it was so voted.

Dr. C. C. Shaw moved that the Resolutions Committee arrange a resolution to be presented at the afternoon meeting, extending greetings from the House of Delegates to the new dean of the University, Dr. H. A. Kemp. This motion was seconded and passed.

Dr. Frost moved that the report of the Nominating Committee be accepted. The motion was seconded and officers elected as reported by the committee.

Dr. E. J. Quinn moved that the meeting be adjourned. The motion was seconded and carried.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 25471

PRESENTATION OF CASE

First Admission. A sixty-three-year-old chief of police was admitted to the hospital complaining of indigestion.

The patient was well until three years before admission when he began to have indigestion, described as a "hollow feeling" in the stomach. This was accompanied by gaseous, sour eructations, was worse at night, and was often relieved by soda. His family physician prescribed crackers and milk between meals and at bed time. He was relieved of his distress until three months before entry when he noted a return of sour eructations with vague epigastric distress, which was relieved by vomiting. On one occasion he vomited food eaten "one week before," but usually the food was that ingested one or two meals earlier; once he noted that the vomitus was blood tinged. These symptoms increased steadily. His bowels were regular with mineral oil, which he took nightly. He had felt poorly for three years and had lost 25 pounds in weight, the loss of 15 of which had occurred in the past year. The family, marital and past histories were noncontributory.

The physical examination revealed a well-developed man who showed evidence of recent weight loss. The skin was dry and loose. The heart and lungs were essentially negative. There was an indefinite non-tender mass palpable just beneath the right costochondral junction. The remaining examination was negative.

The temperature, pulse and respirations were normal.

Examination of the urine was negative. The blood showed a red-cell count of 4,500,000 with 90 per cent hemoglobin, and a white-cell count of 10,300 with 65 per cent polymorphonuclears. A gastric analysis revealed a fasting free-acid level of 28 units, with second and third specimens reading 30 and 41. All gastric and stool guaiac tests were negative. The blood Hinton test was negative. The serum protein was 4.8 gm. per 100 cc., two weeks later it was 7.0 gm.; the serum nonprotein nitrogen and chlorides were normal.

A gastrointestinal series showed a dilated stomach containing a considerable quantity of secretions and small particles of food. Peristalsis was intermittent, sometimes reversed, and the waves were rather weak. No barium passed through the pylorus during fluoroscopic examination. The antrum of the stomach was irregular, and the visible portion of the duodenum was deformed. Reexamination seventeen days later showed a normal esophagus. The stomach was dilated and contained a small quantity of fluid. Barium passed the pylorus with great difficulty in spite of much hyperperistaltic activity of the stomach. There was a 2-cm. area of ulceration on the lesser curvature in the region of the pyloric valve. This crater lay both on the gastric and duodenal sides, slightly more on the latter. The base of the cap was deformed; the apex and second portions were normal. At the end of six hours there was a 50 per cent residue in the stomach, at the end of twenty-four hours, a 10 per cent residue. A gastroscopic examination three days after admission showed that peristalsis was absent. The antrum was well seen down to what appeared to be pylorus, which remained slightly patulous throughout the examination. A small area along the lesser curvature near the pylorus could not be visualized due to angulation. The mucosa throughout was partially covered with adherent barium, but this did not interfere with the diagnosis of any gross lesion. The mucosa showed increased reddening, but there was no verrucous appearance.

The patient ran an essentially uneventful hospital course for nineteen days, after which he was discharged to await further x-ray studies. His symptoms failed to improve on a medical regimen consisting of six feedings, a bland diet, rest, frequent gastric lavage, belladonna and sedation.

Second Admission (two weeks later). At this time an x-ray examination revealed that the degree of pyloric obstruction had increased markedly. The stomach was grossly dilated and atonic, and no barium passed the pylorus during the forty-five minutes of fluoroscopic observation. The area of ulceration involving the pyloric valve and prepyloric area was unchanged.

On the day after admission an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. LANGDON PARSONS: Although there are a good many details lacking in the history, I think it is fair to assume that this man had an ulcer with a history extending back over a period of three years. The diet of milk and crackers prescribed by his physician gave moderate relief, but it is noted that he still felt poorly during the three-year period. His symptoms became increasingly severe to the point where obstructive symptoms appeared, a fact which, I believe, brought

him to the hospital. There had been a moderate amount of vomiting, confirming the suggestion of obstruction. A definite change had occurred in the character of his symptoms. On physical examination we note weight loss, most of which had occurred during the past year. He may have been afraid to eat. The fact that he had the low serum protein responding rapidly to treatment suggests that a dietary factor was involved, possibly merely an inadequate food intake over this period. Despite the history of vomiting there is no evidence of dehydration, and it was evidently not of sufficient severity to affect the level of the nonprotein nitrogen or chlorides. There was no hematemesis, although he did have a little blood-tinged vomitus in one episode. The blood picture was normal, and negative guaiac tests were found not only on the gastric contents but also on the stools. The patient, therefore, had no bleeding from his lesion, which we presume was in the upper gastrointestinal tract.

There are two positive findings: the presence of an indefinite mass and the moderately high acid obtained on gastric analysis. The mass is described as indefinite. It is rather hard to evaluate a mass in this particular locality. A suggestion of an indefinite mass in the epigastrium is often difficult to confirm on subsequent exploration. This finding is of no great significance then except for the fact that the so-called mass was nontender. Thus we are left with a history suggesting ulcer and a moderately high acid discovered on gastric analysis. Our next help comes from the gastrointestinal series where the first examination revealed obvious obstruction at the pylorus, an irregular antrum and a deformed duodenum.

Dr. Aubrey O. Hampton: This is the film of the stomach on the first examination, and this is one on the second. Obviously the stomach was grossly dilated at both examinations — more on the second. The character of the defect in the antrum is probably significant. It is not a smooth round curve as you would expect it to be if this ulcer were in the duodenum or at the pyloric valve. The ulcer is apparently in the cavity of the antrum on both examinations. If the barium was made to flow away from the antrum then the ulcer was visible in that area. The ulcer was larger than is stated in the record. I should think it was nearly 2 cm. in diameter rather than 4 mm.

Dr. Parsons: It makes a good deal of difference to me whether it is in the pyloric ring or the prepyloric area.

Dr. Hampton: We were sure the ulcer involved the stomach. It may have extended into the pyloric valve. This film was taken seventeen days later, and if anything the ulcer is larger.

Dr. Parsons: Seventeen days later further x-rays revealed the same obstruction of the pylorus, an irregular antrum and a deformed duodenum. A 50-per-cent residue was noted in six hours, and a 10-per-cent residue in twenty-four. Hyperactive peristalsis was observed. A 2-cm. ulcer was seen which may have arisen at the pyloric valve or on the gastric side. The crater, however, lay both on the gastric and the duodenal sides of the pylorus. A gastroscopy was done which was chiefly interesting because of what it did not show rather than because of what it did show. There was no evidence of gastritis except for the reddening of the gastric mucosa, and the observer failed to see any lesion of appreciable size or in fact any lesion. One thing I should like to ask Dr. Benedict is why the pylorus was patulous at the time of gastroscopy. There was 50-per-cent residue and nothing seen going through at the time of the fluoroscopic examination and the gastrointestinal series.

Dr. Edward B. Benedict: What was seen may not have been the pylorus; it may have been the prepyloric wave that sometimes appears.

Dr. Parsons: We are dealing with an ulcer which gave symptoms of obvious obstruction — either a duodenal ulcer encroaching on the pylorus, a peptic ulcer occurring at the ring or a prepyloric ulcer. If it was a prepyloric ulcer, was it benign or malignant?

I think we can work up a fairly good history for ulcer. He had a three-year history of symptoms which is certainly suggestive. There was at least partial relief of these symptoms on a medical regime, although the process finally went on to the point of obstruction. The patient doubtless did not adhere any too rigidly to his medical diet. He was a chief of police, and it was stated that he was on a milk and cracker diet. I can conceive of several breaks occurring in such a diet in a patient with that occupation. There was no evidence of anemia. A high acid was found on gastric analysis. There was failure to see the lesion on gastroscopy. The ulceration appeared to extend through the pyloric ring and to involve the duodenum. Finally the patient was discharged from the medical service on an ulcer regime. These are all facts which build up a good case for ulcer, but do they necessarily mean that this patient did not have carcinoma?

First, take the three-year history. I have recently been reviewing the cases of carcinoma of the stomach in this hospital. From the point of view of history the patients can readily be divided into two groups: those who had symptoms for six months and those whose story extended over a year. Of patients who came to gastric resection,

25 per cent of those who had symptoms for six months were alive after five years and 35 per cent of those with symptoms of over a year were alive after the same period. The history does not rule out carcinoma. The weight loss possibly bears out the diagnosis of cancer, although it may have been due to an inadequate food intake. The blood was normal. It is possible to have normal blood with carcinoma of the stomach, and it is rare to find a red-cell count below 3,000,000 or a hemoglobin below 50 per cent. Not all gastric carcinoma patients bleed, and we find that there were negative guaiac tests on the stools. In itself high acid does not necessarily point toward ulcer; we find you can have a high acid in cancer, particularly when the lesion arises in the pyloric area. About 18 per cent of the group of gastric cancer patients had either a normal or a high acid. The most puzzling observation is the fact that this ulceration extended over into the duodenum. At one time we were taught that carcinoma of the stomach did not invade the duodenum; but we now know this is not the case for we have seen it extend as far as 3 cm. on the duodenal side when the primary lesion was in the stomach. So this fact does not rule out carcinoma of the stomach. Did the ulceration occur in the pyloric ring? We have come to regard prepyloric ulcer as cancerous until proved otherwise, but we cannot say the same thing for ulceration occurring in the pyloric valve. No evidence of gastritis was seen on gastroscopy. I believe you would find some evidence of gastritis other than reddening of the mucosa if this were a duodenal ulcer. This is not always true, but I should be rather surprised not to find it.

Dr. Benedict: There was some superficial evidence of gastritis. I intended my description to indicate that.

Dr. Parsons: Finally, no improvement was noted in this patient, either by x-ray or clinically, after his discharge from the hospital on a medical regime. I grant that he returned only two weeks after he had left the hospital; no improvement was noted, however.

I am inclined to think that this patient was operated on for an obstructing ulcer, but I believe that the serial sections of the ulcer will show cancer, possibly a carcinoma in situ. If so it was probably carcinoma in situ from the beginning, thus accounting for the long history. At any rate I believe this patient had an ulcerating carcinoma of the stomach. If the lesion was found to be confined to the stomach he had a 62-per-cent chance of living five years.

Dr. Chester M. Jones: I am sorry Dr. Leland McKittrick is not here. I saw this patient with him, and we went through the same line of reasoning as Dr. Parsons has just outlined. My feeling after we had seen him for a day or two was that we had to consider the diagnosis of cancer and I wrote down on the discharge note: "X-ray studies show a big pyloric lesion and twenty-four-hour stasis. In the absence of pain I am anxious about the diagnosis. I think he will come to operation, and I am a little fearful of cancer. He is to go home for a short time and return for further x-ray studies in two weeks." I did not feel justified in letting him go home except with the stipulation that he return in a short time; he was allowed to go only because of his request.

Another thing to point out is the question of pyloric obstruction. The roentgenologists frequently make a diagnosis of pyloric obstruction only to find a few days later there is no stasis whatever. He had frequent gastric lavages, and the amounts removed by gastric aspiration on March 10, 11, 12, 15 and 22 were 240 cc., 240 cc., 30 cc., 180 cc. and 120 cc. respectively. This proves that the stasis was transient, and the actual diagnosis of pyloric obstruction should have been made with a certain amount of reservation. The fact that the stomach was large is in favor of there having been more or less obstruction for quite some time. On reentry he reported that he had had no pain and had only vomited once in two weeks; x-ray study showed about the same findings as before. We decided the only thing to do was to operate, with the expectation of finding an ulcer and quite probably a cancer. Dr. McKittrick operated on that basis.

Dr. J. H. Means: How much credence do you give to the statement that this patient vomited food eaten one week before?

Dr. Jones: All I can say is that this man had a one-track mind and insisted that it was a correct statement. He was so fearful of discomfort that he had been cutting down his diet for weeks before he came in and had a low serum protein because of it.

Dr. Means: If he had such good acid in his stomach I do not believe any food would be recognizable after a week's interval. I draw the conclusion he must have been mistaken.

Dr. Tracy B. Mallory: I should like to ask Dr. Benedict what other evidence of gastritis he would expect to see in a case with a widely dilated stomach other than reddening of the mucosa. Could you expect hypertrophied rugae in such a stomach?

Dr. Benedict: No, but gastroscopic evidence of gastritis does not depend on hypertrophy alone. It is based on a verrucous appearance, which was not present in this case.

Dr. Jones: Coming back to the question of sta-

sis, I might add that there were two drops of mucus reported by Dr. Benedict at the preliminary drainage.

Preoperative Diagnosis

Prepyloric ulcer?
Carcinoma of the stomach with obstruction?

Dr. Parsons's Diagnosis

Carcinoma of the stomach.

Anatomical Diagnosis

Carcinoma of the pylorus and prepyloric region.

Pathological Discussion

Dr. Mallory: This patient was operated on by Dr. McKittrick who found a readily palpable mass in the region of the pylorus and, without hesitation, did a subtotal gastrectomy. After the specimen was opened a lesion about 2.5 cm. in length and 1 cm. in depth was found which occupied part of the pylorus and prepyloric region. In which area it started I cannot say. There was a fairly deep ulcer crater in the center, and the induration extended through all the layers of the wall even the serosa. On microscopic examination we found frank carcinoma with, I should say, quite typical peptic ulceration in the center of the cancer. It is a very common thing to find true peptic ulceration in a malignant lesion and for that reason among others it is not surprising that the symptomatology may be very confusing.

CASE 25472

Presentation of Case

A forty-year-old Italian truck driver was admitted complaining of periodic pain in the epigastrium.

Thirteen years before admission the patient complained of anorexia, vomiting and pain in the epigastrium. He was treated by an outside physician with a diet and "powders" which "cured" him in one year. He apparently lost and regained some 50 pounds in weight during this time. X-ray films of the stomach taken some time during this illness were reported as negative, and he subsequently experienced only occasional "gas pains." He was able to drink beer and wine and eat well, and he had no trouble similar to the first attack until four years before entry when on one occasion he vomited coffee-grounds material. He remained in bed for two weeks and had no further known symptoms until six months before admission when vomiting, anorexia and epigastric pain again appeared. The pain sometimes radiated to the lower part of the sternum or through to the mid-back, usually developed three to four hours after meals or at night and was relieved by soda, by vomiting or by the ingestion of milk. He frequently vomited about fifteen minutes after eating a meal, the vomitus consisting of ingested food without blood. He was gradually forced to stop taking solid foods, and his weight had dropped 30 to 40 pounds during the six months before admission. He had passed no tarry stools.

The past, family and marital histories were not contributory.

The physical examination revealed a muscular, well-developed man who showed slight evidence of recent weight loss. The findings were essentially negative except for the presence of subjective pain, without tenderness or spasm, located at a point in the mid-epigastrium between the xiphoid and umbilicus. The blood pressure was 120 systolic, 78 diastolic.

The temperature, pulse and respirations were normal.

The examination of the urine was negative, and that of the blood showed a red-cell count of 5,300,000 with 92 per cent hemoglobin, and a white-cell count of 10,700 with 64 per cent polymorphonuclears. On admission the stools were yellow, soft and formed and showed a +++ guaiac test. Another stool examination the day before operation was guaiac negative. A serum protein was 6.6 gm. per 100 cc. X-ray studies of the chest were negative. A gastrointestinal series showed in the immediate prepyloric region a constant narrowing with spasm. There was an irregular ulcer crater 4 to 5 mm. in size in the pylorus, if anything slightly on the prepyloric side. There was convergence of the rugae toward the ulcer, but no evidence of surrounding infiltration.

On the fifth hospital day an operation was performed.

Differential Diagnosis

Dr. Edward B. Benedict: Here we have, as I see it, the problem of an ulcer in the pyloric region or prepyloric region, and we must decide, if we can, whether it is benign or malignant. In any case with the x-ray findings of prepyloric ulcer we have come to believe in this hospital that the lesion should be resected since so many prove to be malignant.

To go over the story a little — he was forty years old. That does not help much. The lesion could be cancer at that age. He was a truck driver. That is a nerve-racking occupation. We see many truck drivers with ulcer. The thirteen-year history points toward ulcer. We associate anorexia more frequently with carcinoma than with ulcer,

but if the patient has an ulcer which is causing obstruction, he naturally loses his appetite. Vomiting may go with obstructing ulcer or carcinoma. The negative x-ray films thirteen years previously do not help us. The possibility is raised that he had gastritis at that time. Gastritis can simulate ulcer in almost every respect and give negative x-ray films. His second attack was four years before entry, when he vomited coffee-grounds material. Vomiting such material may be a symptom of either cancer or ulcer. At the present admission he had pain three to four hours after meals which was relieved by soda and milk. That is characteristic of ulcer, but if there is a small area of cancer in a peptic ulcer one may still get the characteristic ulcer pain and get relief from food. Loss of 30 or 40 pounds in weight may occur in obstructing duodenal ulcer. When the patient does not eat well it will lead to loss of weight, but cancer must be seriously considered. The red-cell count and hemoglobin are essentially normal, which is against advanced cancer but not against a microscopic cancer. Gastric analysis sometimes helps us, but apparently it was not done in this case. Gastroscopy might have helped us, but occasionally there is so much prepyloric spasm one cannot see a prepyloric ulcer or, if it is seen, one cannot always be sure whether it is benign or malignant. Schindler* points out that in gastroscopy the presence of the circulating blood in the living tissue and the presence of a clean base with sharp margins are indicative of benign lesions. Other lesions of the stomach to be considered are benign polyps and lymphoma. With these symptoms and no x-ray evidence of a filling defect a polyp is most unlikely. Lymphoma with an ulceration in it is conceivable but unlikely.

Listing the things in favor of ulcer we can enumerate pain three or four hours after meals, relief by milk and soda, a thirteen-year history, a normal red-cell count and hemoglobin, and x-ray evidence of a very small ulcer with converging rugae close to the pylorus, with no infiltration. In favor of cancer stand anorexia, loss of weight and the x-ray appearance of an ulcer possibly in the prepyloric region, particularly the fact that the crater is described as irregular. None of these things are conclusive of either ulcer or cancer. I should like to hear what Dr. Hampton has to say about the x-ray films.

Dr. Aubrey O. Hampton: The second examination reads a little different from the first examination. In the first the ulcer was thought to be prepyloric and in the second it was thought to be in the pylorus. I believe the second interpretation is the more accurate of the two. Certainly we were able to fill the duodenum, and in this picture here is the stomach, and here the duodenum. It would be quibbling if we did not say that this ulcer is in the pyloric valve. The base of the duodenum is puckered a little as though the lesion involved a little of the duodenum, and the stomach is in spasm proximal to the ulcer, which is here. I think if we are ever able to be sure this ulcer is directly in the valve.

Dr. Benedict: As a matter of fact, I have been leaning all along toward the diagnosis of ulcer. Ulcers in the pylorus are usually duodenal and not malignant; furthermore, there are some prepyloric ulcers that are not malignant. I was recently looking up a case of prepyloric ulcer which was resected and proved to be two benign gastric ulcers, one 4 cm. from the pylorus, and the other 1 cm. That does not alter our opinion that they should all be resected if they are prepyloric. Since this lesion is in the pylorus by x-ray and for the other reasons already stated, I will say it is benign.

Dr. Tracy B. Mallory: Does anyone wish to differ with this opinion?

Dr. Chester M. Jones: I should like to emphasize the importance of a decision to operate rather than the importance of making a diagnosis. An absolute diagnosis is impossible and of minor importance. The decision to resect a lesion that is potentially malignant is the only point to stress in this particular case.

Preoperative Diagnosis

Duodenal ulcer.

Dr. Benedict's Diagnosis

Benign pyloric ulcer with obstruction.

Anatomical Diagnosis

Carcinoma of the stomach with invasion of the duodenum.

Pathological Discussion

Dr. Mallory: This patient was operated on with a preoperative diagnosis of duodenal ulcer, but with the intention of resecting, regardless of the anatomical findings. The ulcer lay in the pylorus but extended from it toward the gastric side for a distance of about 1.5 cm. It was not very large. There was absolutely no induration. In the gross it would have been quite impossible by palpation to have recognized it as being malignant. On microscopic examination we found a large central area of peptic ulceration, but on either side of that and in occasional spots on the floor

*Schindler, R.: *Gastroscopy*. 343 pp. Chicago: University of Chicago Press, 1937.

of the ulcer definite carcinoma was found. Almost all of it was limited to the mucosal layer and in only one spot was there the slightest invasion below the muscularis mucosa. On the other hand it is not a pure carcinoma in situ, because in the mucosal layer there is definite infiltration between persistent normal glands for a considererable distance and this infiltration of the mucosal layer extends a few millimeters into the duodenum.

DR. JONES: Would you be willing to comment on the frequency with which a carcinoma passes the pyloric valve into the duodenum?

DR. MALLORY: For many years all the textbooks of surgery and pathology said that carcinomas almost never passed the pyloric valve. A few years ago Dr. Castleman examined a series of cases in this hospital in order to check that point and came to a very different conclusion.

DR. BENJAMIN CASTLEMAN: About 25 per cent of all the cancers in the region of the antrum show some extension into the duodenum, the distances varying from 3 mm. to 3 cm.* This will be observed only if special care is taken to select blocks for microscopic examination from the extreme margin of the resected specimen.

DR. JONES: This fact would seem to be very important in the event of resection.

*Castleman, B.: Extension of gastric carcinoma into the duodenum. Ann. Surg. **103**:348-352, 1936.

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HOSPITALS AND — HOSPITALS

In the Hospital Number (March 11, 1939) of the *Journal of the American Medical Association*, there are listed certain hospitals as approved for internship and other hospitals as registered but not so approved. One notes with a considerable degree of uneasiness that still other hospitals, not named, were not registered. What the public would like to know is why hospitals are permitted to exist if they are not suitable even for registration.

It is to be noted in the recently published illuminating article by Runnels* concerning obstetric problems that the author limits himself to five conclusions. The first and last are, respectively, that in the United States there has been in recent years a marked reduction in maternal mortality and that, if obstetric conditions were as good in the whole country as they are in one quarter of the country, there would be an annual saving of 2500 lives. The other conclusions concern the great and rapid increase of hospitalization of obstetric patients, the necessity for competent supervision for hospital obstetrics and the great further decrease in maternal mortality in which such supervised hospitalization would result.

This year in Massachusetts there was prolonged discussion before the legislature of the licensing of hospitals, followed by rejection of the proposed bill. It is true that the State already licenses and supervises all hospitals which care for maternity cases, but the standards for license under the present law represent a dangerously low minimum of equipment and fitness. One of the objections to the proposed plan, not always emphasized publicly, was that certain physicians would not be able to earn a living if they could not run their own little hospitals. Regulation by the State would entail so much in the way of equipment, supplies and personnel that the hospital would have to be closed, and thus the physician would lose the chief source of his income. Another objection was that the licensing of hospitals would be just another (useless) restriction on how a doctor should practice medicine. But it is known that abuses have caused a rising tide of feeling to the effect that there should be some control, external to the proprietors, over these institutions, which have become quasi-public in character.

It may be that licensing by the State as proposed by the bill is not the best procedure, but it is intolerable that an incompetent or unscrupulous physician should have an extension of the field of his activity, such as the owning of an institution gives, without more control than is exercised now.

At the hearings on the bill some isolated cases of abuse were cited, but what is needed before control can be exercised wisely and adequately is a more detailed knowledge of the situation as it exists in Massachusetts today. It is the hospitals not registered by the American Medical Association which are the cause for the greatest concern. Perhaps such a state-wide study might be carried on under the auspices of the Massachusetts Medical Society or the Massachusetts Hospital As-

*Runnels, S. C.: An obstetric audit. J. A. M. A. 113:402-408, 1939.

sociation or by the Massachusetts Department of Public Health. In any case the magnitude and character of the problem should be determined accurately before a specific remedy is advocated. The situation is probably much more serious than anyone now realizes.

HOOTON AND THE FALL OF MAN

Earnest A. Hooton, professor of anthropology, Harvard University, amusingly startles the public in an article in *The Atlantic Monthly** concerning man's degenerating evolutionary trends, and takes particularly to task one portion of mankind: the members of the medical profession. Some of his remarks deserve to be repeated and discussed. He says in part:

> Medicine has alleviated suffering and prolonged life, but it has, in so doing, also prolonged suffering and nullified the purging effect of natural selection. It has saved hundreds of thousands of debilitated organisms which are adding to the burden of society by reproducing more and worse offspring.
>
> . . . I am not aware that they [medical men] have taken any united professional stand in favor of birth control, nor in the matter of sterilization of the feeble-minded, the insane, and the criminalistic, nor even in the establishment and enforcement of rigorous medical examinations for persons intending marriage. . . . While they have accumulated vast files of medical histories, they have not, for the most part, learned the elementary methods and principles of accurate scientific recording and are usually incapable of analyzing massed data from which valid general conclusions may be drawn. Although the social sciences and all other biological sciences have long relied upon mathematical statistics as the only dependable means of elucidating quantitative or qualitative data affected by a multiplicity of causes, medical science stands aloof in obdurate and self-satisfied ignorance.

These blows at medicine, strong as they sound, are administered in friendly fashion, for Professor Hooton goes on to give medical science "credit for remarkable achievement in the conquest of disease." One wonders how serious he is when he makes such mischievous remarks as the following: "Medicine today is an extension of the maternal instinct mixed up with scientific techniques. It operates in an odor of sanctity and formaldehyde."

It would require a generous amount of space to comment in full on the conclusions of this article or those incorporated in Professor Hooton's recent work, *Twilight of Man* (New York: G. P. Putnam & Sons, 1939). Many of the conclusions concerning disease are of doubtful validity. Some of the indictments of the medical profession are unquestionably well deserved, many of them demand criticism, and all of them require careful thought. At least it is startling to think that the medical profession may be shouldered with the responsibilities not only of the care of the sick and the prevention of illness but also with the care of society and its ills and with the care of the proper evolution of man!

One reads into his work that Professor Hooton believes that the human race is degenerating. Recent trends of world affairs, indeed, have led many to believe so. Perhaps students of history will not agree that the present state of affairs in the world is abnormal. At any rate it appears that we need more convincing proof that mankind is degenerating or even that protection of the weak has interfered seriously with natural selection. One fact is obvious: mankind has survived. To survive in the face of enormous environmental forces means the presence of strong protective mechanisms in the body. It is hard to believe that man is the weakling that Professor Hooton would have us think.

His suggestion that modern methods of handling large masses of data by machinery should be used more and more by hospitals and medical research institutions deserves comment. Are not these methods merely modern, time-saving devices for recording, classifying and describing? Are they an important part of experimental medicine as it was introduced by Claude Bernard? Would their use ever lead to important medical discoveries such as have occurred for several centuries? William Harvey would never have discovered the circulation of the blood if all he had done was to punch-card the data of Galen. The machine has not been built which can substitute for the human reasoning used in performing a useful physiological experiment. When it is built, then perhaps man can allow his brain to atrophy.

*Hooton, Earnest A.: *The Wages of Biological Sin.* The Atlantic Monthly **164**:435-445, 1939.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

RAYMOND S. TITUS, M.D., *Secretary*
330 Dartmouth Street
Boston

PUERPERAL SEPSIS AT TERM

Mrs. F. B., a twenty-one-year-old para I at term, was admitted to the hospital June 15, 1912, in active labor of two and a half hours' duration.

The patient's past and family histories were not recorded. The last menstrual period began on September 16, 1911, making her due for delivery June 23. The prenatal course had been entirely normal.

The physical examination was normal. The heart was not enlarged; there were no murmurs. The lungs were clear and resonant; there were no rales. The pelvic measurements were normal. The baby was presenting by the breech in the SLA position. The fetal heart was heard best in the left lower quadrant, and its rate was 160.

A simple breech delivery was performed under ether anesthesia when the patient was fully dilated after four hours of labor. There were no lacerations. The baby weighed 6 pounds, 8 ounces, and was in good condition. The placenta was delivered intact; the uterus contracted well, and there was only a normal loss of blood.

The patient had a smooth convalescence until the fourth night after delivery when the temperature rose to 102°F., the pulse to 115, and the respirations to 25. There was moderate tenderness over the fundus of the uterus. The lochia was very foul. The following night the temperature rose to 105°F., and the pulse to 130. A curettage was performed with a dull curet. A large amount of retained secundines was removed. An intra-uterine douche of sterile water was administered, followed by one of alcohol. A uterine culture taken at the time of curettage subsequently revealed colon bacilli and streptococci (type not determined). The patient ran a spiking temperature for the next ten days. She received daily intra-uterine douches of sterile water followed by alcohol.

On July 5, twenty days after delivery a vaginal examination was made. The uterus was of normal size, anterior and freely movable. To the left of the uterus was an indurated, non-tender mass, the size of a lime. The right vault was free. During the ten-day interval following this examination the temperature varied from 99 to 100.2°F., and the pelvic mass increased in size to that of an orange. The patient received hot douches daily. She was discharged home against advice on July 17, 1912. Discharge examination revealed a persistent mass, the size of an apple.

Comment. This case is recorded to illustrate the popular treatment of puerperal infection in 1912. Today cultures would have been taken from the uterus at the onset of the fever, blood cultures would have been taken, and the uterus would have been left entirely alone. Curettage in the absence of hemorrhage is entirely outmoded. It undoubtedly did no good in this case and may well have spread the infection. Daily intra-uterine douches of sterile water followed by alcohol was a common routine at that time. These undoubtedly did no good and are never given nowadays. They were not infrequently followed by chills. When one appreciates that whenever an infection of the uterus exists the infected areas are chiefly within the uterine musculature, one realizes that no matter how much alcohol is used it cannot come in contact with these areas as none of it is retained in the uterine cavity. The induration to the left of the uterus when the patient was discharged was evidence of infection of the left parametrium. Such indurated masses almost never demand surgery unless a pelvic abscess develops, which fortunately is not common. When such cases are treated conservatively, the pelvis usually remains free from infection and sterility rarely ever results.

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

MEDICAL POSTGRADUATE EXTENSION COURSES

The following sessions of the Medical Postgraduate Extension Courses have been arranged for the week beginning November 27:

BARNSTABLE

Sunday, December 3, at 4:00 p.m., at the Cape Cod Hospital, Hyannis. Complications in Obstetrics, Illustrated by Case Histories. Instructor: Christopher J. Duncan. Donald E. Higgins, *Chairman.*

BRISTOL NORTH*

BRISTOL SOUTH (New Bedford Section)

Friday, December 1, at 4:00 p.m., at St. Luke's Hospital, New Bedford. Syphilis in Pregnancy and the Offspring. Instructor: C. Guy Lane. Robert H. Goodwin, *Chairman.*

ESSEX NORTH

Friday, December 1, at 4:30 p.m., at the Lawrence General Hospital, Lawrence. Head and Spine Injuries. Instructor: Walter R. Wegner. John Parr, *Chairman.*

*The course will be omitted November 30 because of Thanksgiving Day.

ESSEX SOUTH

Tuesday, November 28, at 4:00 p.m., in the Conference Room of the Salem Hospital, Salem. Indications for Cesarean Section. Instructor: Robert L. DeNormandie. J. Robert Shaughnessy, *Chairman.*

MIDDLESEX EAST

Tuesday, November 28, at 4:00 p.m., at the Melrose Hospital, Melrose. Head and Spine Injuries. Instructor: Donald Munro. Walter H. Flanders, *Chairman.*

MIDDLESEX NORTH

Friday, December 1, at 4:45 p.m., at St. John's Hospital, Lowell. The Use of Drugs in the Treatment of Childhood Infections. Instructor: Warren R. Sisson. William S. Lawler, *Chairman.*

WORCESTER (Milford Section)

Tuesday, November 28, at 8:30 p.m., in the Nurses' Home of the Milford Hospital, Milford. Common Laboratory Procedures in Pediatrics and Their Interpretation. Instructor: LeRoy D. Fothergill. Joseph Ashkins, *Chairman.*

WORCESTER (Worcester Section)

Friday, December 1, at 8:00 p.m., in the Staff Room of the Worcester City Hospital, Worcester. Complications in Obstetrics, Illustrated by Case Histories. Instructor: Judson A. Smith. George C. Tully, *Chairman.*

WORCESTER NORTH

Friday, December 1, at 4:30 p.m., in the Nurses' Home of the Burbank Hospital, Fitchburg. Surgical Complications in Obstetrics. Instructor: Raymond S. Titus. George P. Keaveny, *Chairman.*

DEATHS

HARRINGTON — MICHAEL W. HARRINGTON, M.D., of Springfield, died November 13. He was in his sixty-seventh year.

Born in Ireland, he came to this country sixty years ago. He studied at Holy Cross College and received his degree at Baltimore Medical College in 1901.

He was a fellow of the Massachusetts Medical Society and the American Medical Association.

MOLINE — CHARLES MOLINE, M.D., of Sunderland, died November 15. He was in his sixty-fourth year.

Born in Motala, Sweden, he came to Sunderland when he was twelve years old. In 1896 he graduated from Williston Seminary. He attended Harvard University and received his degree from the Harvard Medical School in 1903.

He was a fellow of the American Medical Association and the Massachusetts Medical Society, being secretary of the Franklin County District for twenty years.

His widow and two daughters survive him.

OAK — CHARLES A. OAK, M.D., of Lynn, died November 15. He was in his sixty-first year. He was born and received his early education in Boston, and graduated from Harvard Medical School in 1906.

For twenty-five years he was a member of the surgical staff of the Lynn Hospital and had practiced there for thirty years. He was a fellow of the Massachusetts Medical Society and the American Medical Association and a member of the Radiological Society of North America.

His widow, two daughters and a sister survive him.

ROBERTS — SUMNER M. ROBERTS, M.D., of Boston, was fatally injured in an automobile accident on November 19. He was in his forty-second year.

Born in Dedham, he prepared for college at the Country Day School in Newton. He attended Harvard University and received his degree from the Harvard Medical School in 1925. He was an assistant in orthopedic surgery at the Harvard Medical School, a member of the orthopedic staff of the Massachusetts General Hospital, chief surgeon at the Robert Breck Brigham Hospital and a member of the staff of the Faulkner Hospital and of Children's Island in Marblehead.

Dr. Roberts was a fellow of the Massachusetts Medical Society and the American Medical Association. He was president of the Boston Orthopedic Club and held memberships in the American College of Surgeons, the American Academy of Orthopaedic Surgeons and the American Orthopaedic Association.

His widow, a daughter, two sons, his mother, a brother and a sister survive him.

MISCELLANY

VERMONT NEWS

The following new members have been added to the faculty of the University of Vermont College of Medicine: Dr. B. J. A. Bombard, Burlington, associate professor of clinical surgery; Dr. A. F. G. Edgelow, Springfield, Massachusetts, assistant professor of clinical obstetrics; Dr. A. S. C. Hill, Winooski, assistant professor of clinical medicine; Dr. Arthur R. Hogan, Burlington, assistant professor of clinical surgery; Dr. Peter P. Lawlor, Burlington, assistant professor of otolaryngology and rhinology, and clinical instructor in ophthalmology; Dr. Wilhelm Raab, Burlington, assistant professor of clinical medicine; Dr. P. M. Ashton, Springfield, Massachusetts, instructor in clinical obstetrics; Dr. A. P. Barney, Springfield, Massachusetts, instructor in clinical obstetrics; Dr. Nathan R. Caldwell, Burlington, instructor in clinical radiology; Dr. A. J. Crandall, Essex Junction, instructor in clinical surgery; Dr. H. M. Farmer, Burlington, instructor in clinical medicine; Dr. Alfred M. Glickman, Springfield, Massachusetts, instructor in clinical obstetrics; Dr. Theodore H. Harwood, Burlington, instructor in medicine; Dr. Fred S. Kent, Burlington, instructor in clinical medicine; Dr. Robert E. L. Loring, Springfield, Massachusetts, instructor in clinical obstetrics; Dr. Katherine E. McSweeney, Burlington, instructor in clinical medicine; Dr. Watson F. Rogers, Underhill, instructor in clinical medicine; Dr. Stanley S. Stusick, Springfield, Massachusetts, instructor in clinical obstetrics; Dr. Christopher M. Terrien, Burlington, instructor in clinical medicine; Dr. J. G. Thabault, Winooski, instructor in clinical medicine; Dr. L. G. Thabault, Winooski, instructor in surgery; Dr. Frederick C. Thorne, Brandon, instructor in psychiatry; Dr. George C. Tully, Worcester, Massachusetts, instructor in clinical urology; Dr. Fletcher H. White, Burlington, instructor in clinical obstetrics; Dr. Clarence E. Bombard, Burlington, assistant in surgery; Dr. Robert S. Jenks, Burlington, assistant in anatomy; and Dr. John H. McCrea, Burlington, assistant in medicine.

PHRENIC NERVE INTERRUPTION

Phrenic nerve interruption in the treatment of tuberculosis has lately lost much of its former popularity. By some it is condemned as being practically useless, if not actually harmful. A more discriminating judgment of this operation is urged by J. W. Cutler (Phrenic Nerve Interruption. Am. Rev. Tuberc. *40*:26-54, 1939), who has analyzed 122 consecutive phrenic nerve interruptions in his private patients. An abstract of this paper follows:

Claims concerning the value of phrenic nerve interruption are contradictory and confusing. One author reviewed 78 reports involving a total of 7435 operations performed as an independent procedure and found "cures" reported in 23 per cent. On the other hand, Coryllos, citing his own experiences and those of several workers abroad, concluded that the operation is "not efficient, not without danger, and causes a loss of precious time."

This wide divergence of opinion is in good part explained by the type of patient treated — phenomenally good results are in relatively early cases and they would undoubtedly have been obtained from bed-rest alone, while in far-advanced cases and in the presence of large, thick-walled cavities success can rarely be expected.

In a consecutive series of 122 tuberculous patients on whom phrenic nerve interruption was performed, it was done on 106 as an independent collapse measure. Many stages and varieties of tuberculosis are represented. Sexes are about equally distributed. The operation was done 60 times on the left side and 62 on the right. In 65 the interruption was temporary, in 57 permanent.

Evaluation of the operation should be based primarily on the changes that follow in the lung under consideration, as determined primarily by comparative x-ray findings, and not necessarily by the ultimate fate of the patient. The time element, following operation, is of extreme importance. The good results of phrenic nerve interruption become evident within the first six months. Late results are more difficult to define; therefore, a three-to-five-year postoperative interval, as a basis for late results, is not unreasonable.

The evaluation of phrenic nerve interruption is discussed under four main headings: the value of the operation as an independent collapse measure; the value as an adjunct to other collapse measures; complications of the operation; and temporary as contrasted with permanent phrenic nerve interruption, and their corresponding indications and contraindications.

In retrospect, the cases are classified as "apparently suitable" and "unsuitable." Unsuitable cases include: apical cavities 3 or more cm. in diameter, for the operation is useless in the attempt to close apical cavities in which the apex has become more or less excavated and adherent to the thoracic wall; dense fibrotic lesions with embedded cavities; pneumonic consolidations; acute infiltrations. In this series there were 30 patients with lesions deemed in retrospect as unsuitable for the operation. The contraindications, in the sense that no benefit will follow, cannot however be considered absolute, for occasionally a distinctly good result followed.

Seventy-one patients fell into the "apparently suitable" category and were evaluated as follows:

Unimproved (52 per cent). No material x-ray evidence of improvement in the tuberculous lesions was noted within three to six months after the operation, or an actual increase in the disease. Lack of improvement was observed in all kinds of cases with "apparently suitable" lesions, including both cases of early limited infiltrations without x-ray evidence of cavity and cases of advanced disease.

Improved (34 per cent). Cavity was either closed or reduced in size or there was x-ray evidence of significant clearing with lessening of toxemia and improvement in well being. However, in only 14 of the 24 cases in this group, did the improvement result in the stabilization of the lesion so that no further therapy was required. In the remaining 10, improvement, marked at first, was in time followed by serious relapse.

Cleared (14 per cent). Clearing of the disease in the lung except for some fibrous strands and a few small, sharply defined, moderately dense, spots. There were cavities of varying sizes in 8 and infiltration without x-ray evidence of cavity in 2. The result followed so shortly after operation and in such manner as to leave little doubt that the paralysis of the diaphragm was the responsible factor. The lungs have remained clear over an average period of more than 6 years after operation.

No concrete conclusions could be reached as to the type of case among the "apparently suitable" patients in which the operation can be undertaken with reasonable assurance of success. Good results were obtained in advanced disease and in unexpected situations. On the other hand, failures were encountered in minimal cases. In general, good results were observed more frequently when the major lesion was situated below the clavicle, and when the cavity was isolated, thin-walled and surrounded by nearly normal lung tissue.

The relative value of phrenic nerve interruption as an alternative to artificial pneumothorax and thoracoplasty, is considered. In the majority of cases in which phrenic nerve interruption was used as an alternative to pneumothorax the operation was either a useless undertaking or relapse followed an initial improvement. In those cases in which bilateral pneumothorax ultimately became necessary, selective collapse could be established in only 12 out of 28 patients. Time wasted on phrenic nerve interruption was largely responsible for the formation of extensive adhesions. Phrenic nerve surgery should not be looked on as a substitute for pneumothorax, but must be regarded as a supplementary form of therapy.

More serious is the question of phrenic nerve interruption in preference to thoracoplasty. Of 31 patients in this series suitable for an immediate thoracoplasty, but subjected to phrenic nerve interruption in the hope of avoiding thoracoplasty, 3 died from hemoptysis and 3 from progressive tuberculosis and 7 more became hopeless invalids. In retrospect, these tragedies might have been avoided had thoracoplasty been performed promptly when conditions were most favorable. The important thing is not to resort to a phrenic nerve operation when thoracoplasty is plainly indicated, and not to delay thoracoplasty beyond the time when the phrenic nerve operation has accomplished its maximum good.

Phrenic nerve interruption was carried out also in 16 patients either as an adjunct to other collapse measures or in the treatment of certain complications of pneumothorax therapy including: ineffective pneumothorax, hemoptysis, troublesome cough, discontinued pneumothorax therapy, spontaneous pneumothorax, empyema cavities. The operation accomplished the desired result in about one third of these patients.

Complications of phrenic nerve interruption must be taken into consideration. In the present series, significant complications attributable to the operation were encountered in 6, with death in 2. Cardiac failure, which accounted for the 2 deaths, was the outstanding compli-

cation. Other important complications were interference with the cough mechanism (2 patients) and gastric disturbances (belching and a sense of fullness in the stomach), annoying but not serious (3 patients). The fact remains, however, that the treatment of tuberculosis does not always permit a safe and sure choice of therapy. Phrenic nerve interruption may, in individual cases, prove to be accompanied by the least risk.

Both temporary and permanent phrenic nerve interruption have their place. A temporary phrenic nerve interruption is indicated when the problem is of an emergency nature, as in hemorrhage or active disease requiring immediate collapse therapy when other collapse measures cannot be instituted at the moment, and when other collapse measures, such as pneumothorax or thoracoplasty, are in prospect. A permanent phrenic nerve operation is indicated when the operation is carried out as the sole therapeutic measure in the attempt to cure the patient after other collapse procedures have been considered unsuitable, or are plainly contraindicated.

The danger today is not that too many phrenic nerve operations will be performed or that they will be undertaken in an indiscriminate manner, but that the operation will be discarded. This would be unfortunate, for phrenic nerve interruption appears to have value in 15 to 25 per cent of patients. At times it may be the simplest means for saving a patient's life. The operation, however, should be restricted to properly selected cases. — Reprinted from *Tuberculosis Abstracts*, November, 1939.

MASSACHUSETTS PSYCHIATRIC SOCIETY

The annual meeting and dinner of the Massachusetts Psychiatric Society was held on Thursday, November 2, at 6:30 p.m. at the University Club, Boston. Dr. Karl Bowman, formerly associated with the Boston Psychopathic Hospital and now director of the Psychiatric Division, Bellevue Hospital, New York City, spoke about the Desmond Bill, a law recently passed in New York relative to the psychiatric examination of prisoners.

The officers elected for 1939–1940 are as follows: president, Dr. William A. Bryan; vice-president, Dr. Harlan L. Paine; secretary-treasurer, Dr. W. Franklin Wood; councilors, Drs. Harry C. Solomon and Clifton T. Perkins.

NOTICES

BOSTON DISPENSARY

A talk on "The Psychology of the Hard of Hearing" will be given at the Boston Dispensary by Mr. John C. G. Loring on Friday, December 1, at 9 a.m.

CARNEY HOSPITAL

The monthly meeting of the John T. Bottomley Society will be held at the Out-Patient Department of Carney Hospital on Tuesday, November 28, at 11 a.m.

PROGRAM

"Coramine," a film produced by Audio Productions, Incorporated, with pharmacological scenes prepared by Ciba Research Laboratories, will be shown.

WILLIAM J. MACDONALD, M.D., *Secretary*.

PETER BENT BRIGHAM HOSPITAL

A joint medical and surgical clinic at the Peter Bent Brigham Hospital will be held on Wednesday, November 29, from 2 to 4 p.m. Drs. Elliott C. Cutler and Soma Weiss will speak on "The Unconscious Patient: Syncope." A clinicopathological conference, conducted by Dr. Elliott C. Cutler, will take place from 4 to 5 p.m.

Physicians and students are cordially invited to attend.

ELLIOTT C. CUTLER, M.D., *Secretary*.

BOSTON DOCTORS' SYMPHONY ORCHESTRA

The Boston Doctors' Symphony Orchestra will rehearse under Alexander Theide, former concertmaster with the Cleveland Symphony Orchestra and the Philadelphia Symphony Orchestra, every Thursday at 8:30 p.m., in Studio A, Station WMEX, 70 Brookline Avenue, Boston. Those interested in becoming members should communicate with Dr. Julius Loman, Pelham Hall Hotel, Brookline (BEA 2430).

MASSACHUSETTS GENERAL HOSPITAL

A meeting of the Hospital Research Council will be held in the Ether Dome of the Massachusetts General Hospital, on Tuesday, November 28, at 5:00 p.m.

PROGRAM

Coagulation Factors. Dr. J. D. Stewart.

Changes in Blood Pressure and Pulse Rate on Stimulation of the Autonomic Nuclei in the Human Hypothalamus. Dr. J. C. White.

Studies of Muscle Function in Rheumatoid Arthritis. Drs. A. O. Ludwig, C. L. Short and R. S. Schwab.

HENRY K. BEECHER, M.D., *Secretary*.

SUFFOLK DISTRICT MEDICAL SOCIETY

There will be a meeting of the Suffolk District Medical Society at the Boston Medical Library, 8 Fenway, on Wednesday evening, November 29, at 8:15.

PROGRAM

The Theory and Practice of Massive Dose Chemotherapy by the Intravenous Drip Method in the Treatment of Early Syphilis. Drs. William Leifer, Louis Chargin and Harold T. Hyman.

MILTON H. CLIFFORD, M.D., *Secretary*.

MASSACHUSETTS DEPARTMENT OF CIVIL SERVICE AND REGISTRATION

MEDICAL ADVISER, DEPARTMENT OF INDUSTRIAL ACCIDENTS

Director of State Civil Service, Ulysses J. Lupien, has recently announced that a competitive examination is to be held on January 6 to find eligibles for appointment to the position of Medical Adviser, Department of Industrial Accidents. The minimum salary is $4200 a year; the maximum, $5100. The duties are as follows: to examine medical testimony given by physicians and technicians at formal proceedings; to make physical examinations of injured workmen and submit opinions and diagnoses as to disability and causal relation to injury; to advise the Industrial Accident Board as to the selection of competent industrial-disease referees and impartial physicians; to interpret medical problems and terminology for the members of the Board; to systemize and supervise the personnel of the medical unit of the department. The appointees will be permitted to carry on private practice to such ex-

tent as is approved by the Department of Industrial Accidents.

The entrance requirements are as follows: applicants must be physicians licensed to practice medicine by the Massachusetts Board of Registration in Medicine and must be or must have been members of the medical or surgical staff of a hospital approved by the American College of Surgeons.

The subjects and weights are as follows: training and experience, 2; practical questions, 3; total, 5. Applicants must obtain at least 70 per cent in each subject of the examination in order to become eligible. Physical fitness is to be determined by physical examination.

The last date for filing applications is Saturday, December 23, 1939, at noon.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The regular clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held at the hospital on Thursday, December 7, at 7:15 p.m.

Dr. Ella P. Cahill will be the chairman in charge of the meeting and Dr. Edgar C. Yerbury, director of mental hygiene, will be the guest speaker.

LAURA H. MUIR, M.D., *Chairman.*

NORFOLK DISTRICT MEDICAL SOCIETY

The next meeting of the Norfolk District Medical Society will be held in the Hotel Somerset, Boston, Tuesday, November 28, at 8:15 p.m.

PROGRAM

A Symposium of the Work of Certain Committees of the Massachusetts Medical Society.

The Committee on Ethics and Discipline. Dr. Robert L. DeNormandie.

The Committee on Public Relations. Dr. Michael A. Tighe.

The Committee on State and National Legislation. Dr. Charles C. Lund.

Discussion.

Collation.

FRANK S. CRUICKSHANK, M.D., *Secretary.*

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS, UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	ORTHOPEDIC CONSULTANT
Lowell	December 1	Albert H. Brewster
Salem	December 4	Harold C. Bean
Haverhill	December 6	William T. Green
Gardner	December 12	Mark H. Rogers
Brockton	December 14	George W. Van Gorder
Worcester	December 15	John W. O'Meara
Pittsfield	December 18	Francis A. Slowick
Northampton	December 20	Garry deN. Hough, Jr.
Fall River	December 21	Eugene A. McCarthy
Hyannis	December 22	Paul L. Norton

METROPOLITAN STATE HOSPITAL

A clinicopathological staff conference will be held at the Metropolitan State Hospital, Waltham, on Wednesday, November 29, at 8:00 p.m.

PROGRAM

A Case Presenting Special Psychiatric and Neurological Features from Both the Clinical and Pathological Aspects. Dr. Clementine McKeon and Dr. Richard C. Wadsworth. Discussed by Dr. Ira T. Nathanson and Dr. Paul I. Yakovlev.

All interested physicians are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, NOVEMBER 27

MONDAY, NOVEMBER 27

*12:15 p.m.–1:15 p.m. Clinicopathological conference. Dr. S. Burt Wolbach, Peter Bent Brigham Hospital amphitheater.

*8:15 p.m. New England Heart Association. Massachusetts General Hospital.

TUESDAY, NOVEMBER 28

*9–10 a.m. X-ray Demonstration. Dr. Alice Ettinger. Joseph H. Pratt Diagnostic Hospital.

*10 a.m.–12:30 p.m. Boston Dispensary tumor clinic.

11 a.m. Carney Hospital. John T. Bottomley Society.

*12:15 p.m.–1:15 p.m. X-ray conference. Dr. Merrill C. Sosman. Peter Bent Brigham Hospital amphitheater.

5 p.m. Massachusetts General Hospital. Hospital Research Council.

8:15 p.m. Norfolk District Medical Society. Hotel Somerset, Boston.

*8:15 p.m. "Visualization of Placenta in Utero." Dr. A. Louis Dippel. Boston Lying-in Hospital.

WEDNESDAY, NOVEMBER 29

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12 m. Clinicopathological conference. Children's Hospital amphitheater.

*2 p.m.–4 p.m. Joint medical and surgical clinic. Peter Bent Brigham Hospital.

8:15 p.m. Suffolk District Medical Society. Boston Medical Library. 8 Fenway, Boston.

FRIDAY, DECEMBER 1

9 a.m. "The Psychology of the Hard of Hearing." John C. G. Loring. Boston Dispensary.

*10 a.m.–12:30 p.m. Boston Dispensary tumor clinic.

12 m. Clinical meeting of the Children's Medical Service, Massachusetts General Hospital. Ether Dome.

*12 m. Urological conference at the Massachusetts General Hospital, lower amphitheater, Out-Patient Department.

SATURDAY, DECEMBER 2

*10 a.m.–12 m. Medical staff rounds of the Peter Bent Brigham Hospital. Conducted by Dr. Soma Weiss.

*Open to the medical profession.

NOVEMBER 24 — Boston Dispensary. Luncheon meeting of the clinical staff. Page 758, issue of November 9.

NOVEMBER 25 — Joseph H. Pratt Diagnostic Hospital. Page 758, issue of November 9.

NOVEMBER 27 — New England Heart Association. Page 798, issue of November 16.

NOVEMBER 28 — Boston Lying-in Hospital. Page 797, issue of November 16.

NOVEMBER 28 — Massachusetts General Hospital. Hospital Research Council. Page 840.

NOVEMBER 28 — Carney Hospital. John T. Bottomley Society. Page 840.

NOVEMBER 29 — Peter Bent Brigham Hospital. Joint medical and surgical clinic. Page 840.

NOVEMBER 29 — Metropolitan State Hospital. Notice above.

DECEMBER 1 — Boston Dispensary. "The Psychology of the Hard of Hearing." Mr. John C. G. Loring. Page 840.

DECEMBER 2 — American Board of Obstetrics and Gynecology. Page 1019, issue of June 15.

DECEMBER 5 — Massachusetts Hospital Association. Page 798, issue of November 16.

DECEMBER 6 — Wachusett Medical Improvement Society. Page 798, issue of November 16.

DECEMBER 6 — New England Obstetrical and Gynecological Society. Page 759, issue of November 9.

DECEMBER 7 — New England Hospital for Women and Children. Notice above.

DECEMBER 8 — William Harvey Society. Page 676, issue of October 26.

DECEMBER 14 — Pentucket Association of Physicians. 8:30 p.m., Hotel Bartlett, Haverhill.

JANUARY 6, JUNE 8–11, 1940 — American Board of Obstetrics and Gynecology. Page 160, issue of July 27, and page 798, issue of November 16.

JANUARY 22–25, 1940 — American Academy of Orthopaedic Surgeons. Hotel Statler, Boston.

FEBRUARY 11–14 — International College of Surgeons. Page 759, issue of November 9.

MARCH 2, JUNE 8 and 10 — American Board of Ophthalmology. Page 719, issue of November 2.

MARCH 7–9, 1940 — The New England Hospital Association. Hotel Statler, Boston.

MAY 14, 1940 — Pharmacopoeial Convention. Page 894, issue of May 25.

JUNE 7–9, 1940 — American Board of Obstetrics and Gynecology. Page 1019, issue of June 15.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

JANUARY 3, 1940 — Semi-annual meeting. Combined meeting with Essex South. Danvers State Hospital, Hathorne. 7 p.m.

ESSEX SOUTH

DECEMBER 6 — "Pyelonephritis and Its Relation to Other Inflammatory Diseases of the Kidney." Dr. Soma Weiss. Salem Hospital, Salem.

JANUARY 3, 1940 — "Head Injuries." Dr. John S. Hodgson. Danvers State Hospital, Hathorne.

FEBRUARY 14 — "Cough, Sputum, Hemoptysis — How shall they be investigated?" Dr. Reeve H. Betts. Essex Sanatorium, Middleton.

MARCH 6 — "Experimental and Clinical Considerations of Sulfanilamide Treatment of Hemolytic Streptococcal Infections." Dr. Champ Lyons. Lynn Hospital, Lynn.

APRIL 3 — Addison Gilbert Hospital, Gloucester.

MAY 8 — Annual meeting. Salem Country Club, Peabody.

HAMPSHIRE

JANUARY 10, 1940.

MARCH 13.

MAY 8.

All meetings are held at 11:30 a.m. at the Cooley Dickinson Hospital, Northampton.

MIDDLESEX EAST

JANUARY 10, 1940.

MARCH 20.

MAY 15.

Meetings are held at 12:15 p.m. at the Unicorn Country Club, Stoneham.

NORFOLK

NOVEMBER 28 — Page 841.

PLYMOUTH

JANUARY 18, 1940 — Brockton Hospital, Brockton.

MARCH 21 — Goddard Hospital, Brockton.

APRIL 18 — State Farm.

MAY 16 — Lakeville Sanatorium, Lakeville.

SUFFOLK

NOVEMBER 29 — Scientific meeting. Treatment of Syphilis. Dr. Harold T. Hyman, Dr. Louis Chargin, and Dr. William Leifer, of New York City. Page 840.

JANUARY 31, 1940 — Scientific meeting. Subject to be announced later.

MARCH 27 — Scientific meeting. Symposium on Ulcerative Colitis and Diarrheas. Under the direction of Dr. Chester M. Jones.

APRIL 24 — Annual meeting in conjunction with the Boston Medical Library. Election of officers. Program and speakers to be announced later.

BOOKS RECEIVED FOR REVIEW

Principles of Development: A text in experimental embryology. Paul Weiss. 601 pp. New York: Henry Holt & Co., 1939. $5.00.

Health for New York City's Millions: An account of activities of the Department of Health of the City of New York for 1938 with comparative vital statistics tables. Edited by Savel Zimand. 295 pp. New York: Department of Health, 1939.

Blood Groups and Blood Transfusion. Alexander S. Wiener. Second edition. 306 pp. Springfield, Illinois, and Baltimore: Charles C Thomas, 1939. $5.00.

Psychobiology and Psychiatry: A textbook of normal and abnormal human behavior. Wendell Muncie. 739 pp. St. Louis: C. V. Mosby Co., 1939. $8.00.

Textbook of Nervous Diseases. Robert Bing. Translated and enlarged by Webb Haymaker. From fifth German edition. 838 pp. St. Louis: C. V. Mosby Co., 1939. $10.00.

Medical Record Visiting List or Physicians' Diary for 1940. Revised. Baltimore: William Wood & Co., 1939. $2.00.

Ophthalmology. Clio Medica 20. Burton Chance. 240 pp. New York: Paul B. Hoeber, Inc., 1939. $2.00.

Tumors of the Skin: Benign and malignant. Joseph J. Eller. 607 pp. Philadelphia: Lea & Febiger, 1939. $10.00.

The Vitamins: A symposium, arranged under the auspices of the Council on Pharmacy and Chemistry and the Council on Foods of the American Medical Association. 637 pp. Chicago: American Medical Association, 1939, $1.50.

Sixty-first Annual Report of the Department of Health of the State of New Jersey, 1938. 406 pp. Trenton: Department of Health, New Jersey.

Fractures. Paul B. Magnuson. Third edition. 511 pp. Philadelphia, Montreal, London: J. B. Lippincott Co., 1939. $5.00.

A Handbook on Diabetes Mellitus and Its Modern Treatment. J. P. Bose. Third edition. 272 pp. Calcutta: Thacker, Spink & Co., Ltd., 1939. Rs. 7-8.

Psychopathia Sexualis: A medico-forensic study. Richard von Krafft-Ebing. Twelfth edition. 626 pp. New York: Pioneer Publications, Inc., 1939. $3.00.

BOOK REVIEWS

Nitrous Oxide-Oxygen Anesthesia: McKesson-Clement viewpoint and technique. F. W. Clement. 274 pp. Philadelphia: Lea & Febiger, 1939. $4.00.

This book "is dedicated as a memorial to the life, work and achievements of Dr. E. I. McKesson" and sets forth his philosophy and the technic of methods for the use of nitrous oxide and oxygen which he worked out during his lifetime. It is an authoritative treatise on this method of anesthesia, but its value as a practical guide for others is somewhat lessened by the fact that in the detailed description of technic the use of the McKesson machine only is described.

A complete explanation and rationalization of the signs of anesthesia is given. Respiration and muscular signs are stressed while phonation and color are shown to be deceptive and unreliable as they bear no relation to the depth of anesthesia in different individuals. Premedication, charting and signs of the onset of shock are well presented.

An explanation of the role of carbon dioxide in respiration is treated in a most thorough manner. It is also shown that there is no "fixed relationship between cyanosis and physiological anoxemia, a fact of great importance in the clinical interpretation of cyanosis." The famous "secondary saturation" is carefully described, explained and declared to be less dangerous than essential oxygen want during prolonged deep narcosis.

Dr. Clement reiterates the importance of a clear airway in many of his discussions, especially those concerning special operations. He shows clearly that obstruction to breathing causes alterations of the normal physiologic processes. His methods of treating such obstructions are rational and simple, and show great clinical knowledge. Although the author gives elaborate instruction for administering nitrous oxide and oxygen for major abdominal operations, he admits that even the McKesson technic, in his hands, will not produce the relaxation obtained with a good ether or spinal anesthesia.

There is no doubt left in the reader's mind regarding the clinical ability or knowledge of the author in dealing with nitrous oxide and oxygen anesthesia. His presentation of the subject is most convincing, and the book is a fitting tribute to the late Dr. McKesson and should preserve for anesthetists the knowledge which he so painstakingly acquired. It should be read and preferably owned by every anesthetist who at any time uses this type of anesthesia.

Headache and Head Pains: A ready reference manual for physicians. Walton F. Dutton. 301 pp. Philadelphia: F. A. Davis Co., 1939. $4.50.

The primary purpose of the author of this book is to bring the medical profession to an appreciation of the importance and significance of headache. He believes that "no sources of pain compare in frequency to those symptoms in the large majority of patients who seek medical aid," and, second, that the major concern of the scientific practitioner is centered in the problems of diagnosis, underlying pathology and therapeutic technic in dealing with disease with the implication that the cause of the symptoms must be discovered if cure or amelioration is to be brought about.

He deplores the custom of self-medication for the relief of symptoms which too often leads to postponement of the essential management of a case, with disastrous results. A good description of the anatomy and functions of the several systems of nerves prepares the reader for the adoption of certain defined methods of study in attempts to solve the etiologic problems in cases with different types of headache.

The greater portion of the book is given to brief descriptions of nearly two hundred and fifty diseases and functional disturbances in which headache appears as a prominent symptom; consideration is given to remedies designed to relieve suffering.

This book is worthy of a place in the physician's library because it is well written and covers the ground, but the question may be raised as to whether the emphasis placed on the relief of a symptom may not divert the attention of those doctors who are not well trained from an adequate study of a disease which can only be properly treated on knowledge of its pathology.

Peripheral Vascular Diseases: Diagnosis and treatment. William S. Collens and Nathan D. Wilensky. 243 pp. Springfield, Illinois, and Baltimore: Charles C Thomas, 1939. $4.50.

This monograph handles effectively, though by no means exhaustively, the diagnosis and treatment of peripheral arteriosclerosis and thromboangiitis obliterans. For the pathology of arteriosclerosis, the authors lean heavily on Winternitz's theory of local fault in the vaso vasorum. The best chapters of the book are those on symptoms and signs, methods of examination, and the general care of the patient. The authors review all methods of increasing the circulation to the extremities. However, they devote most space to intermittent venous compression, the treatment which they have devised. This is well done, with detailed case reports illustrating the method. Other types of treatment are not so well handled. Various forms of heat are proposed without reference to the possible deleterious effects, except for burns. Moreover they offer no help in evaluating such unusual quoted methods as the subcutaneous introduction of oxygen and carbon dioxide or the intra-arterial injection of medicinal agents.

The book fails to live up to its avowed comprehensive nature. Unusual but important organic lesions such as cervical rib and periarteritis nodosa are given brief and indecisive mention. Functional disorders are better described, but could stand more detailed presentation.

The addition of a chapter on the treatment of varicose ulcers by intermittent venous occlusion, without any other discussion of the varicose problem, hardly seems justified in a text devoted to arterial diseases.

Operative Orthopedics. Willis C. Campbell. 1154 pp. St. Louis: The C. V. Mosby Co., 1939. $12.50.

The author has had an extensive operative experience and therefore is well equipped to produce a book of this type.

The introductory chapter is confined to a consideration of the physiology and pathology of bones and joints; then follows a chapter on the apparatus used in the Campbell Clinic.

The rest of the book is devoted to a description of various orthopedic conditions and of the different types of operative procedures that are standardized and commonly used. The division of subjects follows rather closely the author's textbook of orthopedic surgery and includes fresh fractures, malunited fractures and non-union.

The chapter on arthroplasty is very complete, as would be expected, because of the author's personal interest in this subject and his extensive writings. It is chiefly a summary of his own work, although he describes the technic of other authors.

The chapter devoted to the correction of deformities due to infantile paralysis is well done and timely since it constitutes an important part of orthopedic surgery. The author describes the various types of standard operations, giving credit to the different authors and using some of their drawings and cuts. At the same time he has emphasized the methods that he commonly uses.

The reproductions of x-ray plates and the drawings are adequate and freely used, and they complement the text very well. There is a bibliography at the end of each chapter and a very good index at the end of the book. This is a very good and timely book.

A Textbook of Surgery. By American authors. Edited by Frederick Christopher. Second edition, revised. 1695 pp. Philadelphia and London: W. B. Saunders Co., 1939. $10.00.

Since its first appearance in 1936 this volume has become the favorite textbook of surgery of many American medical students. There are one hundred and eighty-eight contributors, almost all of them associated in a teaching capacity with medical schools. In its pages the whole of surgery, including gynecology, urology and orthopedics, is covered. Of course, no single volume can encompass the entire field of surgery today, and it is questionable if the term "textbook" is wholly advisable. Perhaps *An Introduction to Surgery* would be more suitable; as such its excellence is unquestioned. Most of the criticism which a careful survey of the volume brings forth concerns omissions rather than errors. Some of those which struck the reviewer as of particular importance follow.

The question of sprains and contusions is dismissed in a few paragraphs. These common injuries might well have received more attention.

In the section on trigeminal neuralgia, alcohol injection is summarily dismissed as of little benefit, and operation advised as soon as the diagnosis is established. It should be mentioned that many neurological surgeons believe that alcohol injections should precede operation

whenever possible so that the patient will have actual experience with anesthesia of the face and be able to weigh the disadvantage of numbness against the advantage of freedom from pain. No mention is made of the ingenious apparatus of Kirschner for the coagulation of the gasserian ganglion. This has not been used in this country but has apparently been very successful in Europe.

In the section on sciatica no mention is made of the operation of Ober: division of the fascia lata. Although a relatively new procedure, it has been received with considerable favor and should at least be mentioned as a method of treatment for this otherwise often baffling condition.

In the section on cancer of the breast the procedure of roentgen castration of all patients who are still menstruating is dismissed in a paragraph and is not recommended as a routine. This procedure is now accepted as of great value and is practiced as a routine in most Eastern clinics.

The section on chronic fat necrosis of the female breast is likely to leave the student with the impression that it can be differentiated from carcinoma in most cases. This is far from true, as any surgeon of experience can testify. Reference should be made to the work of Dunphy in this connection and it should be emphasized that the condition is almost invariably indistinguishable, in the gross form, from carcinoma.

The described method for carrying out closed drainage in cases of empyema of the chest will almost inevitably result in pyopneumothorax. It has long been established that the presence of air in an empyema cavity facilitates the absorption of bacterial toxins and should be avoided.

The reviewer was astonished to find in the otherwise adequate discussion of acute appendicitis no mention of referred or "rebound" tenderness which is generally considered to be one of the most important, if not the most important, single sign of the disease.

In the thirty-seventh chapter, entitled "Aseptic Surgical Technic," the traditional sterilization of linen in sealed steel drums is described and illustrated. The inadequacy and dangers inherent in such methods of sterilization have been well established by the researches of Walter and others. Furthermore, 90 per cent alcohol is advocated as a rinse for the surgeon's hands after scrubbing and for the removal of iodine from the operative field. It has been known for at least fifty years that 95 per cent alcohol is of very little value as an antiseptic; it is far inferior to 70 per cent alcohol, which itself is not particularly good.

These errors, however, are of relatively minor importance and do not detract from the fundamental excellence of the volume as a whole. Undoubtedly they will be corrected in future editions. The popularity of the book is deserved and should continue.

Provoked Alimentary Hyperglycemia: The mechanism of the tolerance test. Joseph M. Flint. 37 pp. *The Effect of the Macallum-Laughton Duodenal Extract Upon Hypophyseal Diabetes.* Joseph M. Flint and Louis Michaud. 77 pp. London, Ontario: A. B. Macallum, 1939.

The first of these two articles, which are bound in one volume, is a summary of literature and also, to some extent, of experimental observations dealing with the ordinary glucose tolerance test. Using the angiostomy method, the author concluded that in the ordinary glucose tolerance test there is a shift of function between the liver and intestines at the beginning and at the end of the reaction, such that the liver and intestines exchange roles as yielding and retaining organs in relation to the blood sugar. Thus, on the appearance of carbohydrate in the duodenum, absorption of sugar begins and its concentration in the intestine mounts until it passes the retention point, when glucose is yielded to the portal radicals. The increase in sugar concentration in the portal blood is the stimulus that induces the liver to reduce its yield of sugar to the zero point and to begin to retain sugar. Then as the blood sugar falls below normal, the relation is reversed again. He regards diabetic tolerance tests as exaggerations of the same factors in regulation.

In the second article observations making use of the Macallum-Laughton extract of the duodenum are reported. This extract is regarded as a stabilizing and synergizing factor to insulin, and an antagonist to the anterior portion of the pituitary gland, tending to anchor the blood sugar to normal levels and maintain its stability. When given to diabetic patients by mouth or combined with insulin, it may overcome the insulin resistance and the impaired utilization which are present in hypophyseal diabetes. To the reviewer, it seems that distinctions between hypophyseal and pancreatic diabetes have less significance than formerly, because Young has demonstrated that the production of diabetes by means of injections of crude pituitary extract is brought about by destruction of the islands of Langerhans.

Both articles contain discussions of many of the classical experiments dealing with carbohydrate metabolism and particularly the recent experiments of Young. The actual experimental data reported, however, could be discussed more briefly with advantage to the reader.

Clinical Diagnosis by Laboratory Methods: A working manual of clinical pathology. James C. Todd and Arthur H. Sanford. Ninth edition. 841 pp. Philadelphia and London: W. B. Saunders Co., 1939. $6.00.

This, the ninth edition of a well-known and standard textbook on clinical laboratory methods, has been carefully brought up to date. Some obsolete procedures in urinalysis have been deleted, and new tests have been included, such as the complete technic of Bodansky for the determination of phosphate and phosphatase, the complete technic of Power and Wakefield for sulfates, the hippuric acid test for liver function, the technic for the determination of serum lipase, and that for cevitamic acid and sulfanilamide in blood and urine.

There has been a complete revision of the material on serodiagnostic tests for syphilis. Besides this, many minor changes and several illustrations have been added. In regard to illustrations, in the new colored frontispiece the blues are too brilliant and the reds are too pale, as is so often the case. This plate does not compare with some of the older plates still retained in the book.

The volume is a most useful one, and is doubtless one of the best we have at present on the subject.

The New International Clinics: Original contributions: clinics; and evaluated reviews of current advances in the medical arts. Edited by George M. Piersol. Vol. 2, N. S. 2. 321 pp. Philadelphia, Montreal and New York: J. B. Lippincott Co., 1939. $3.00.

This volume covers a wide range of subjects. Vitamins from the neurological and psychiatrical aspects are discussed, and there is an article on pellagra. Treatment of anemia, the functions of the pituitary gland and cancers of the male reproductive organs are among the large group of excellent contributions by well-known authors.